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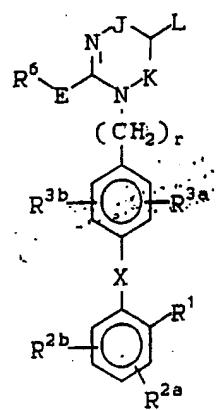
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㉖ Substituted quinazolinones as angiotensin II antagonists.

㉗ Novel substituted quinazolinones of the formula (I), which are useful as angiotension II antagonists, are disclosed.

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(I)

SUBSTITUTED QUINAZOLINONES AS ANGIOTENSIN II ANTAGONISTS

INTRODUCTION OF THE INVENTION

This invention relates to novel substituted quinazolinone compounds and derivatives thereof which are useful as angiotensin II antagonists in the treatment of elevated blood pressure and congestive heart failure.

5 Thus, the substituted quinazolinone compounds of the invention are useful as antihypertensives.

BACKGROUND OF THE INVENTION

10 Renin-angiotensin system (RAS) plays a central role in the regulation of normal blood pressure and seems to be critically involved in hypertension development and maintenance as well as congestive heart failure. Angiotensin II (All), an octapeptide hormone is produced mainly in the blood during the cleavage of angiotensin I by angiotensin converting enzyme (ACE) localized on the endothelium of blood vessels of lung, kidney, and many other organs, and is the end product of the RAS. All is a powerful arterial 15 vasoconstrictor that exerts its action by interacting with specific receptors present on cell membranes. One of the possible modes of controlling the RAS is angiotensin II receptor antagonism. Several peptide analogs of All are known to inhibit the effect of this hormone by competitively blocking the receptors, but their experimental and clinical applications have been limited by their partial agonist activity and lack of oral absorption [M. Antonaccio. *Clin. Exp. Hypertens.* A4, 27-46 (1982); D. H. P. Streeten and G. H. Anderson, 20 Jr. - *Handbook of Hypertension, Clinical Pharmacology of Antihypertensive Drugs*, ed. A. E. Doyle, Vol. 5, pp. 246-271, Elsevier Science Publisher, Amsterdam, The Netherlands, 1984].

Recently, several non-peptide compounds have been described as All antagonists. Illustrative of such compounds are those disclosed in U.S. Patents 4,207,324; 4,340,598; 4,576,958; 4,582,847 and 4,880,804 in European Patent Applications 028,834; 245,637; 253,310; and 291,969; and in articles by A.T. Chiu, et al. [25 *Eur. J. Pharm. Exp. Therap.*, 157, 13-21 (1988)] and by P.C. Wong, et al. [*J. Pharm. Exp. Therap.*, 247, 1-7(1988), *Hypertension*, 13, 489-497 (1989)]. All of the U.S. Patents, European Patent Applications 028,834 and 253,310 and the two articles disclose substituted imidazole compounds which are generally bonded through a lower alkyl bridge to a substituted phenyl. European Patent Application 245,637 discloses derivatives of 4,5,6,7-tetrahydro-2H-imidazo[4,5-c]pyridine-6-carboxylic acid and analogs thereof as antihypertensive agents.

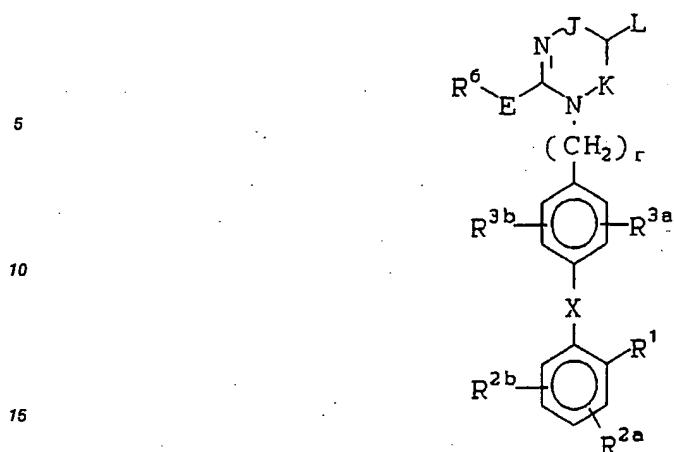
DETAILED DESCRIPTION OF THE INVENTION

35 This invention relates to novel substituted quinazolinone compounds and derivatives thereof which are useful as angiotensin II antagonists, as antihypertensives, in the treatment of congestive heart failure and in the treatment of elevated intraocular pressure. The compounds of this invention have the general formula (I):

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45

50



(I)

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wherein:

L is connected with J or K to form an aromatic ring as defined below;

25 J is -C(=M)- or J and L are connected together to form a 6 carbon aromatic ring substituted with R7a, R7b, R8a and R8b, provided that only one of J and K is -C(=M)-;

K is -C(=M)- or K and L are connected together to form a 6 carbon aromatic ring substituted with R7a, R7b, R8a and R8b, provided that only one of J and K is -C(=M)-;

M is O or NR22;

R1 is

30 (a) -CO2R4,

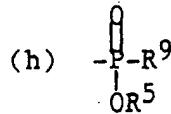
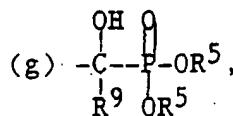
(b) -SO3R5,

(c) -NHSO2CF3,

(d) -PO(OR5)2,

(e) -SO2-NH-R9,

35 (f) -CONHOR5,



(i) -SO2NH-heteroaryl as defined below,

(j) -CH2SO2NH-heteroaryl as defined below,

(k) -SO2NH-CO-R23,

50 (l) -CH2SO2NH-CO-R23,

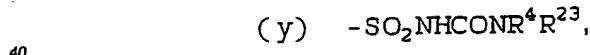
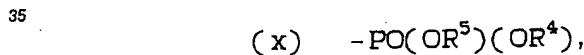
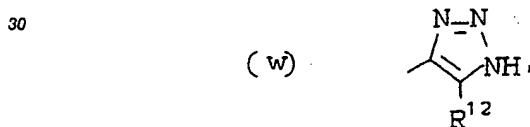
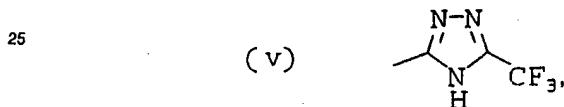
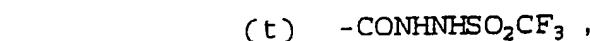
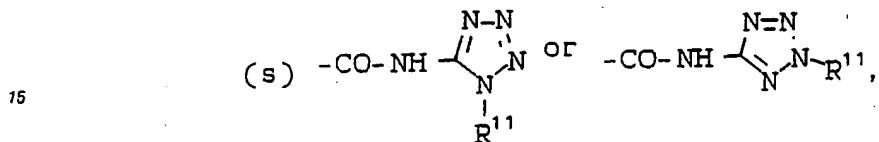
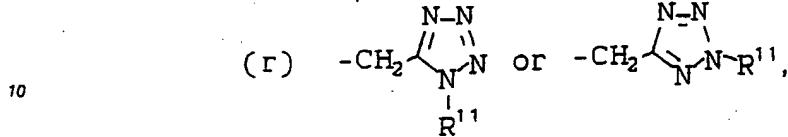
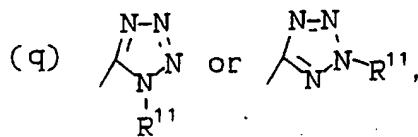
(m) -CONH-SO2R23,

(n) -CH2CONH-SO2R23,

(o) -NHSO2NHCO-R23,

(p) -NHCONHSO2-R23,

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wherein heteroaryl is an unsubstituted, monosubstituted or disubstituted five or six membered aromatic ring which can optionally contain from 1 to 3 heteroatoms selected from the group consisting of O, N or S and wherein the substituents are members selected from the group consisting of -OH, -SH, -C₁-C₄-alkyl, -C₁-C₄-alkoxy, -CF₃, halo (Cl, Br, F, I), -NO₂, -CO₂H, -CO₂-(C₁-C₄-alkyl), -NH₂, -NH(C₁-C₄-alkyl) and -N(C₁-C₄-alkyl)₂;

R²¹ and R²² are each independently (a) H,

(b) halogen, (Cl, Br, I, F)

(c) NO₂,

(d) NH₂,

(e) C₁-C₄-alkylamino,

(f) di(C₁-C₄-alkyl)amino

(g) SO₂NHR⁸,

(h) CF₃,

(i) C₁-C₆-alkyl,

(j) C₁-C₆-alkoxy,

(k) C₁-C₆-alkyl-S-,

(l) C₂-C₆-alkenyl,

- (m) C_2 - C_6 -alkynyl;
- (n) aryl as defined below,
- (o) aryl(C_1 - C_4 alkyl),
- (p) C_3 - C_7 -cycloalkyl;

5 R_{3a} is

- (a) H,
- (b) halo (Cl, Br, I, F)
- (c) C_1 - C_6 -alkyl,
- (d) C_1 - C_6 -alkoxy,

10 (e) C_1 C_6 -alkoxyalkyl;

R^{3b} is

- (a) H,
- (b) halo (Cl, Br, I, F)
- (c) NO₂,

15 (d) C_1 - C_6 -alkyl,

- (e) C_1 - C_6 -acyloxy,
- (f) C_3 - C_7 -cycloalkyl,
- (g) C_1 - C_6 -alkoxy,
- (h) -NHSO₂R⁴,

20 (i) hydroxy(C_1 - C_4 -alkyl),

- (j) aryl(C_1 - C_4 -alkyl),
- (k) C_1 - C_4 -alkylthio,
- (l) C_1 - C_4 -alkyl sulfinyl,
- (m) C_1 - C_4 -alkyl sulfonyl,

25 (n) NH₂,

- (o) C_1 - C_4 -alkylamino,
- (p) di(C_1 - C_4 -alkyl)amino,
- (q) fluoro- C_1 - C_4 -alkyl,
- (r) -SO₂-NHR⁹,

30 (s) aryl as defined below,

- (t) furyl,
- (u) CF₃,
- (v) C_2 - C_6 -alkenyl,
- (w) C_2 - C_6 -alkynyl;

35 wherein aryl is phenyl or naphthyl optionally substituted with one or two substituents selected from the group consisting of halogen(Cl, Br, I, F), N(R⁴)₂, CO₂R⁴, C_1 - C_6 -alkyl, C_1 - C_4 -alkoxy, NO₂, CF₃, C_1 - C_4 -alkylthio, or OH;

R⁴ is H, aryl as defined above or straight chain or branched C_1 - C_6 alkyl optionally substituted with aryl as defined above;

40 R^{4a} is aryl as defined above or straight chain or branched C_1 - C_6 -alkyl optionally substituted with aryl as defined above

R⁵ is

45

$$H, -CH-O-C(R^{4a})^2$$

E is a single bond, -NR¹³(CH₂)_s-, -S(O)_x(CH₂)_s-where x is 0 to 2 and s is 0 to 5, -CH(OH)-, -O-, CO-;

R⁶ is

50 (a) aryl as defined above optionally substituted with 1 or 2 substituents selected from the group consisting of halo (Cl, Br, I, F) O- C_1 - C_4 -alkyl, C_1 - C_4 -alkyl, -NO₂, -CF₃, -SO₂NR⁹R¹⁰, -S- C_1 - C_4 -alkyl, -OH, -NH₂, C_3 - C_7 -cycloalkyl, C_3 - C_{10} -alkenyl;

(b) straight chain or branched C_1 - C_6 -alkyl, C_2 - C_5 -alkenyl or C_2 - C_5 -alkynyl each of which can be optionally substituted with a substituent selected from the group consisting of aryl as defined above, C_3 - C_7 cycloalkyl, halo (Cl, Br, I, F), CF₃, CF₂CF₃, -NH₂, NH(C_1 - C_4 -alkyl), -OR⁴, -N(C₁-C₄-alkyl)₂, -NH-SO₂R⁴, -COOR⁴, -SO₂NHR⁹;

55 (c) an unsubstituted, monosubstituted or disubstituted heteroaromatic 5 or 6 membered cyclic ring which can contain one or two members selected from the group consisting of N, O, S, and wherein the

substituents are members selected from the group consisting of -OH, -SH, C₁-C₄-alkyl, C₁-C₄-alkoxy, -CF₃, halo (Cl, Br, I, F), or NO₂;

(d) C₃-C₇-cycloalkyl;

(e) perfluoro-C₁-C₄-alkyl,

6 (f) H;

R^{7a} and R^{7b} are independently

(a) H,

(b) straight chain or branched C₁-C₆-alkyl, C₂-C₆-alkenyl or C₂-C₆-alkynyl,

(c) halo(Cl, Br, I, F)

10 (d) CF₃, or

(e) when R^{7a} and R^{7b} are bonded to adjacent carbon atoms, they can be joined to form a phenyl ring;

R^{8a} and R^{8b} are independently

(a) H,

(b) C₁-C₆-alkyl optionally substituted with a substituent selected from the group consisting of -OH,

15 -guanidino, C₁-C₄-alkoxy, -N(R⁴)₂, COOR⁴, -CON(R⁴)₂, -O-COR⁴, -aryl, -heteroaryl, -S(O)_xR²³, -tetrazol-5-yl, -CONHSO₂R²³, -SO₂NH-heteroaryl, -SO₂NHCOR²³, -PO(OR⁴)₂, -PO(OR⁴)R⁹ -SO₂NH-CN, -NR¹⁰COOR²³,

(c) -CO-aryl,

(d) -C₃-C₇-cycloalkyl,

(e) halo (Cl, Br, I, F),

20 (f) -OH,

(g) -OPR²³,

(h) -C₁-C₄-perfluoroalkyl,

(i) -S(O)_xR²³,

(j) -COOR⁴,

25 (k) -SO₃H,

(l) -NR⁴R²³,

(m) -NR⁴COR²³,

(n) -NR⁴COOR²³,

(o) -SO₂NR⁹R¹⁰,

30 (p) -NO₂,

(q) -N(R⁴)SO₂R²³,

(r) -NR⁴CONR⁴R²³,

(s)

35



40 (t) -aryl or -heteroaryl as defined above,

(u) -NHSO₂CF₃,

(v) SO₂NH-heteroaryl,

(w) -SO₂NHCOR²³,

(x) -CONHSO₂R²³,

45 (y) -PO(OR⁴)₂,

(z) -PO(OR⁴)R⁹,

(aa) -tetrazol-5-yl,

(bb) -CONH(tetrazol-5-yl),

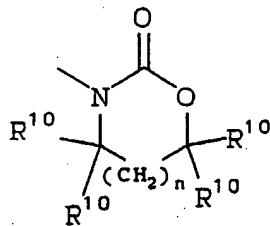
(cc) -COR⁴,

50 (dd) SO²-NHCN

(ee)

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10



where n=0 or 1.

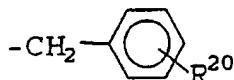
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R9 is H, C1-C5-alkyl, aryl or arylmethyl;

R10 is H, C1-C4-alkyl;

R11 is H, C1-C5-alkyl, C1-C4-alkenyl, C1-C4-alkoxy alkyl, or

20



25

R12 is -CN, -NO2 or -CO2R4;

R13 is H, (C1-C4-alkyl)CO-, C1-C6-alkyl, allyl, C3-C6-cycloalkyl, aryl or arylmethyl;

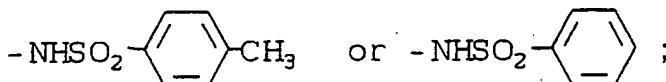
R14 is H, C1-C8-alkyl, C1-C8-perfluoroalkyl, C3-C6-cycloalkyl, aryl or arylmethyl;

R15 is H, C1-C6-alkyl;

R16 is H, C1-C6-alkyl, C3-C6-cycloalkyl, aryl or arylmethyl;

30

R17 is -NR9R10, -OR10, -NHCONH2, -NHCSNH2,



35

R18 and R19 are independently C1-C4-alkyl or taken together are -(CH2)q- where q is 2 or 3;

R20 is H, -NO2, -NH2, -OH or -OCH3;

R21 is H, aryl, or C1-C4-alkyl optionally substituted with aryl, -NH2, -NH(C1-C4-alkyl), -N(C1-C4-alkyl)2, -CO2R4, -OH, -SO3H, -SO2NH2;

40

R22 is

(a) aryl as defined above,

(b) heteroaryl as defined above,

(c) C1-C4-alkyl optionally substituted with a substituent selected from the group consisting of aryl as defined above, heteroaryl as defined above, -OH, -NH2, -NH(C1-C4-alkyl), -N(C1-C4-alkyl)2, -CO2R4, halo(Cl, Br, F, I), -CF3;

45

R23 is

(a) aryl as defined above,

(b) heteroaryl as defined above,

(c) C3-C7-cycloalkyl,

50

(d) C1-C6-alkyl optionally substituted with a substituent selected from the group consisting of aryl as defined above, heteroaryl as defined above, -OH, -SH, C1-C4-alkyl, -O(C1-C4-alkyl), -S(C1-C4-alkyl), -CF3, halo (Cl, Br, F, I), -NO2, -CO2H, CO2-C1-C4-alkyl, -NH2, -NH(C1-C4-alkyl), -N(C1-C4-alkyl)2, -PO3H2, -PO(OH)(O-C1-C4-alkyl), -PO(OR4)R9;

55

(e) perfluoro-C1-C4-alkyl;

X is

(a) a carbon-carbon single bond,

(b) -CO-,

(c) -O-,

(d) -S-,

(e) $\begin{array}{c} -N- \\ | \\ R^{13} \end{array}$

5

(f) $\begin{array}{c} -CON- \\ | \\ R^{15} \end{array}$

10

(g) $\begin{array}{c} -NCO- \\ | \\ R^{15} \end{array}$ (h) -OCH₂-,(i) -CH₂O-15 (j) -SCH₂-,(k) -CH₂S-,(l) -NHC(R⁹)(R¹⁰),(m) -NR⁹SO₂-,(n) -SO₂NR⁹-,20 (o) -C(R⁹)(R¹⁰)NH-,

(p) -CH=CH-,

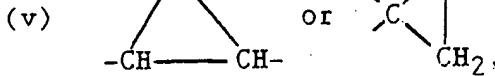
(q) -CF=CF-,

(r) -CH=CF-,

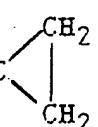
(s) -CF=CH-,

25 (t) -CH₂CH₂-,(u) -CF₂CF₂-,

30



or



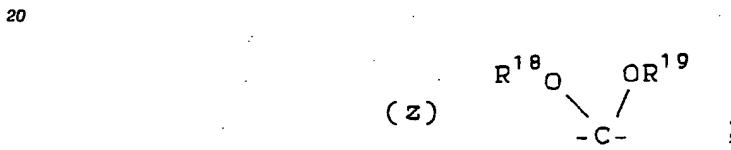
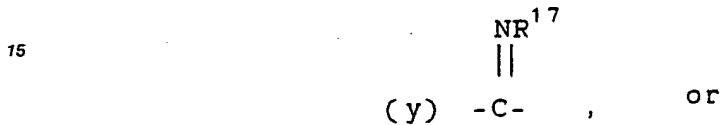
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r is 1 or 2; and
the pharmaceutically acceptable salts thereof.

One embodiment of the compounds of formula (I) are those compounds wherein:

30 J is $-\text{C}(\text{O})-$;
K and L are connected together to form a 6 carbon aromatic ring substituted with R^{7a} , R^{7b} , R^{8a} and R^{8b} ;
R¹ is
(a) $-\text{COOH}$,

35 (b)



(c) $-\text{NH}-\text{SO}_2\text{CF}_3$;
(d) $-\text{SO}_2\text{NH}$ -heteroaryl as defined above,
50 (e) $-\text{CH}_2\text{SO}_2\text{NH}$ -heteroaryl as defined above,
(f) $-\text{SO}_2\text{NH}-\text{CO}-\text{R}^{23}$,
(g) $-\text{CH}_2\text{SO}_2\text{NH}-\text{CO}-\text{R}^{23}$,
(h) $-\text{CONH}-\text{SO}_2\text{R}^{23}$,
(i) $-\text{CH}_2\text{CONH}-\text{SO}_2\text{R}^{23}$,
55 (j) $-\text{NHSO}_2\text{NHCO}-\text{R}^{23}$,
(k) $-\text{NHCONHSO}_2-\text{R}^{23}$,
R^{2a} is H;
R^{2b} is H, F, Cl, CF₃, C₁-C₆-alkyl, C₂-C₄-alkenyl, or C₂-C₄-alkynyl;

R^{3a} is H;R^{3b} is H, F, Cl, CF₃, C₁-C₄-alkyl, C₂-C₄-alkenyl, C₂-C₄-alkynyl, C₅-C₆-cycloalkyl, COOCH₃, -COOC₂H₅, -SO₂-CH₃, NH₂, -N(C₁-C₄-alkyl)₂ or -NH-SO₂CH₃;

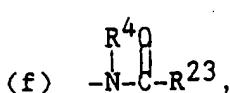
E is a single bond, -O- or -S-;

5 R⁶ is(a) C₁-C₅ alkyl optionally substituted with a substituent selected from the group consisting of C₃-C₅-cycloalkyl, Cl, CF₃, CCl₃, -O-CH₃, -OC₂H₅, -S-CH₃, -S-C₂H₅, phenyl, or F;(b) C₂-C₅-alkenyl or C₂-C₅-alkynyl; or,(c) C₃-C₅-cycloalkyl;10 R^{7a} and R^{7b} are each H;R^{8a} and R^{8b} are independently

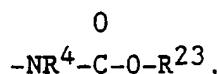
(a) H,

(b) C₁-C₄-alkyl optionally substituted with COOR⁴, OCOR^{4a}, OH, or aryl;(c) C₂-C₄-alkenyl,

15 (d) -OH,

(e) -NO₂,(g) -C₁-C₄-alkoxy

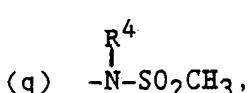
25 (h)

(i) -NR⁴R²³,

(j) halo(Cl, F, Br),

(k) -CF₃,(l) -CO₂R⁴,

35 (m) -CO-aryl as defined above,

(n) -S(O)_x-C₁-C₄-alkyl,(o) -SO₂-NH-C₁-C₄-alkyl,(p) -SO₂-NH-aryl as defined above,

(r) aryl as defined above,

45 (s) -NR⁴CONR⁴R²³;

X is a single bond;

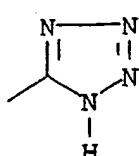
r is one.

In a class of this embodiment are those compounds of Formula (I) wherein:

R¹ is (a) -COOH,

50

(b)



- (c) -NH-SO₂-CF₃,
- (d) -SO₂NH-heteroaryl as defined above.
- (e) -SO₂NH-CO-R²³,
- (f) -CONH-SO₂R²³.

5 E is a single bond;

r is one,

R^{2a}, R^{2b}, R^{3a} and R^{3b} are each H, -C₁-C₆-alkyl, -C₂-C₄-alkynyl -Cl, -F, -NO₂, -CF₃;

R⁶ is -C₁-C₄-alkyl, -cyclopropyl, -CH₂CH₂CH₂CF₃,

-CH₂CH₂CF₃, -C₂-C₅-alkenyl, -cyclopropylmethyl.

10 R^{8a} and R^{8b} are each independently H, -C₁-C₄-alkyl, -NO₂, -NR⁴R²³, -OCH₃, -NR⁴COOR²³, -Cl, -CH₂COOH, -S(O)_xC₁-C₄-alkyl, NR¹⁰CONR⁴R²³, CH₂OCO(C₁-C₄-alkyl), NR⁴COR²³, CO₂R⁴, -F.

In a subclass are those compounds of Formula (I) wherein:

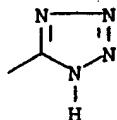
R¹ is

- (a) COOH,

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(b)

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(c) -SO₂NHCOR²³,

25 (d) -CONHSO₂R²³,

(e) -NHSO₂CF₃;

R^{2a}, R^{2b}, R^{3a} and R^{3b} are each H, -C₁-C₄-alkyl, -Cl or F;

R⁶ is -n-propyl, ethyl, -n-butyl, -trans-2-but enyl, CH₂CH₂CF₃, -CH₂CH₂CH₂CF₃, -cyclopropyl, -cyclopropylmethyl;

30 R^{8a} and R^{8b} are each independently H, -NO₂, -C₁-C₄-alkyl, -NH₂, -NHCOCH₃, -S(O)_x(C₁-C₄-alkyl), -N(CH₃)-₂, -OCH₃, -NHCOCH₂NH₂, -NHCOCH₂N(CH₃)₂, -COOH, -COOCH₃, -CH₂OCOCH₃, Cl, -CH₂COOCH₃, -N-(R⁴)CON(R⁴)₂, -N(R⁴)CO₂R⁴, -CH₂COOH, -OCH₃, CH₂OH, NHMe;

Exemplifying this subclass are the following compounds:

(1) 2-Butyl-1-[(2'-carboxybiphen-4-yl) methyl]quinazolin-4(1H)-one;

35 (2) 2-Butyl-1-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(1H)-one;

(3) 2-propyl-1-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(1H)-one;

(4) 2-Butyl-6-methyl-1-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(1H)-one;

(5) 2-Butyl-6-dimethylamino-1-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(1H)-one;

(6) 2-Butyl-5-methyl-1-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(1H)-one;

40 (7) 2-Butyl-7-methyl-1-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(1H)-one;

(8) 2-Butyl-6-nitro-1-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(1H)-one;

(9) 2-Butyl-8-methyl-1-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(1H)-one; and,

(10) 2-Butyl-5-carboxy-1-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(1H)-one.

In a second embodiment are those compounds of Formula (I) wherein:

45 K is -C(O);

J and L are connected together to form a 6 carbon aromatic ring substituted with R^{7a}, R^{7b}, R^{8a} and R^{8b}; and, the class and sub-class of this embodiment are as defined above.

Exemplifying this subclass are the following compounds:

(1) 2-Butyl-3-[(2'-carboxybiphen-4-yl)methyl]quinazolin-4(3H)-one;

50 (2) 2-Butyl-3-[(2'-carboxybiphen-4-yl)methyl]-5-methylquinazolin-4(3H)-one;

(3) 2-Butyl-3-[(2'-carboxybiphen-4-yl)methyl]naphtho[2',3-e]quinazolin-4(3H)-one;

(4) 2-Butyl-3-[(2'-carboxybiphen-4-yl)methyl]-7-methylquinazolin-4(3H)-one;

(5) 2-Butyl-3-[(2'-carboxybiphen-4-yl)methyl]-8-methylquinazolin-4(3H)-one;

(6) 2-Butyl-3-[(2'-carboxybiphen-4-yl)methyl]-6-methylquinazolin-4(3H)-one;

55 (7) 2-Butyl-3-[(2'-carboxybiphen-4-yl)methyl]-6-nitroquinazolin-4(3H)-one;

(8) 2-Butyl-3-[(2'-carboxybiphen-4-yl)methyl]-6,8-dimethylquinazolin-4(3H)-one;

(9) 6-Amino-2-butyl-3-[(2'-carboxybiphen-4-yl)methyl]quinazolin-4(3H)-one;

(10) 6-Acetamido-2-butyl-3-[(2'-carboxybiphen-4-yl)methyl]quinazolin-4(3H)-one;

(11) 2-Butyl-3-[(2'-carboxybiphen-4-yl)methyl]-6-isopropylquinazolin-4(3H)-one;
 (12) 2-Butyl-6-ethyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 (13) 2-Butyl-7-chloro-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 (14) 2-Butyl-6-isopropyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 5 (15) 2-Butyl-6-methyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 (16) 2-Butyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 (17) 6-Methyl-2-propyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 10 (18) 2-Butyl-6-(N-isobutyloxycarbonyl)amino-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 (19) 2-Butyl-6-(N-methyl-N-isobutyloxycarbonyl)amino-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 15 (20) 2-Butyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]-6-thiomethylquinazolin-4(3H)-one;
 (21) 2-Butyl-6-methylsulfonyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 (22) 2-Propyl-6-(N-methyl-N-isobutyloxycarbonyl)amino-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 20 (23) 2-Cyclopropyl-6-(N-methyl-N-isopropylloxycarbonyl)amino-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 (24) (N-Benzyl)amino-2-butyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]-6-quinoxolin-4(3H)-one;
 (25) 6-Acetamido-2-butyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 (26) 2-Butyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]-6-valeroylamidoquinazolin-4(3H)-one;
 25 (27) 2-Butyl-6-(carbobenzoyloxy-N-methyl)amino-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 (28) 2-Butyl-6-(N-carbobenzoyloxy)amino-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 (29) 2-Butyl-6-hydroxymethyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 (30) 2-Butyl-5-hydroxymethyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 30 (31) 2-Butyl-6-(N-methyl)amino-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 (32) 2-n-Butyl-6-(N,N-dimethyl)amino-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 (33) 2-Butyl-6-methoxy-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 (34) 2-Butyl-6-(N-glycyl)amino-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 (35) 2-Butyl-6-(N-(N,N-dimethylamino)glycyl)amino-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 35 (36) 2-Butyl-6-(N-isopropylcarbamoyl)amino-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 (37) 6-(N-isopropylcarbamoyl)amino-2-propyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 (38) 6-(N-Ethyl-N-isobutyloxycarbonyl)-amino-2-propyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 40 (39) 2-Butyl-6-methylsulfinyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 (40) 2-Butyl-6-propylsulfinyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 (41) 6-Acetoxyethyl-2-butyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 (42) 2-Butyl-6-carboxy-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 (43) 2-Butyl-6-carbomethoxy-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 45 (44) 5-Acetoxyethyl-2-butyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 (45) 6-(N-Methyl-N-isopropylcarbamoyl)-amino-2-propyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 (46) 2-Butyl-6-(N-methyl-N-(isopropyl-N-methylcarbamoyl)amino-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 50 (47) 2-Butyl-5-carboxy-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 (48) 2-Butyl-5-carbomethoxy-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 (49) 2-Butyl-5-carbomethoxymethyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 (50) 2-Butyl-5-carbomethoxy-6-methyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 (51) 2-(trans-2-Butenyl)-6-methylsulfinyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 55 (52) 6-Methylsulfinyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]-2-(3,3,3-trifluoropropyl)quinazolin-4(3H)-one;
 (53) 6-Methylsulfinyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]-2-(4,4,4-trifluorobutyl)quinazolin-4(3H)-one;
 (54) 2-Butyl-6-methyl-3-[(2'-(N-phenylsulfonyl)carboxamidobiphen-4-yl)methyl]quinazolin-4(3H)-one;
 (55) 2-Butyl-6-(N-isopropylcarbamoyl)amino-3-[(2'-(N-phenylsulfonyl)carboxamidobiphen-4-yl)methyl]quinazolin-4(3H)-one;
 (56) 2-Butyl-5-carboxy-3-[(2'-(N-methylsulfonyl)carboxamidobiphen-4-yl)methyl]quinazolin-4(3H)-one;
 (57) 3-[(2'-(N-Acetyl)sulfonamidobiphen-4-yl)methyl]-2-butyl-5-carbomethoxyquinazolin-4(3H)-one;
 (58) 3-[(2'-(N-Benzoyl)sulfonamidobiphen-4-yl)methyl]-2-butyl-6-isopropylquinazolin-4(3H)-one;
 (59) 2-Butyl-6-isopropyl-3-[(2'-(N-trifluoromethyl)sulfonamidobiphen-4-yl)methyl]quinazolin-4(3H)-one;

(60) 2-Butyl-6-methyl-3-[(2'-trifluoromethylsulfonamidobiphen-4-yl)methyl]quinazolin-4(3H)-one;
 (61) 6-Amino-2-butyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 (62) 2-Butyl-6-isopropyl-3-[(2'-(N-pyrimidin-2-yl)sulfonamidobiphen-4-yl)methyl]quinazolin-4(3H)-one;
 (63) 2-Butyl-6-isopropyl-3-[(2'-(N-1,3,5-triazin-2-yl)sulfonamidobiphen-4-yl)methyl]quinazolin-4(3H)-one;
 (64) 3-(2'-(N-Acetyl)sulfonamidomethylbiphen-4-yl)methyl-2-butyl-6-isopropylquinazolin-4(3H)-one;
 (65) 6-(N-Methyl-N-isobutyloxycarbonyl)amino-2-propyl-3-[(5'-propyl-2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 (66) 2-Butyl-6-(N-methyl-N-isobutyloxycarbonyl)amino-3-[(5'-propyl-2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 (67) [(5'-Allyl-2'-(tetrazol-5-yl)biphen-4-yl)methyl]-2-propyl-6-(N-methyl-N-isobutyloxycarbonyl)-amino-3-quinazolin-4(3H)-one;
 (68) [(5'-Allyl-2'-(tetrazol-5-yl)biphen-4-yl)methyl]-2-butyl-6-(N-methyl-N-isobutyloxycarbonyl)-amino-3-quinazolin-4(3H)-one;
 (69) 6-(N-methyl-N-isobutyloxycarbonyl)-amino-3-[(5'-phenyl-2'-(tetrazol-5-yl)biphen-4-yl)methyl]-2-propylquinazolin-4(3H)-one;
 (70) 2-Butyl-6-(N-methyl-N-isobutyloxycarbonyl)amino-3-[(5'-phenyl-2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 (71) 3-[(4-Chloro-2'-(tetrazol-5-yl)biphen-4-yl)methyl]-2-propyl-6-(N-methyl-N-isobutyloxycarbonyl)-aminoquinazolin-4(3H)-one;
 (72) 2-Butyl-3-[(4'-chloro-2'-(tetrazol-5-yl)biphen-4-yl)methyl]-6-(N-methyl-N-isobutyloxycarbonyl)-aminoquinazolin-4(3H)-one;
 (73) 3-[4'-Fluoro-(2'-(tetrazol-5-yl)biphen-4-yl)methyl]-6-(N-methyl-N-isobutyloxycarbonyl)amino-2-propylquinazolin-4(3H)-one;
 (74) 2-Butyl-3-[(4'-fluoro-2'-(tetrazol-5-yl)biphen-4-yl)methyl]-6-(N-methyl-N-isobutyloxycarbonyl)aminoquinazolin-4(3H)-one;
 (75) 2-Butyl-6-nitro-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 (76) 6-Amino-2-butyl-3-[(2'-(tetrazol-5-yl)biphen-4-methyl)quinazolin-4(3H)-one;
 (77) 6-(N-Butyl-N-isobutyloxycarbonyl)-amino-2-propyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one;
 (78) 2-Butyl-3-(4'-fluoro-2'-(tetrazol-5-yl)biphen-4-yl)methyl-6-isopropylquinazolin-4(3H)-one; and,
 (79) 2-Butyl-3-[2'-(N-benzenesulfonyl)carboxamido-biphen-4-yl)methyl]-6-isopropylquinazolin-4(3H)-one;

In a third embodiment are those compounds of Formula (I) wherein:

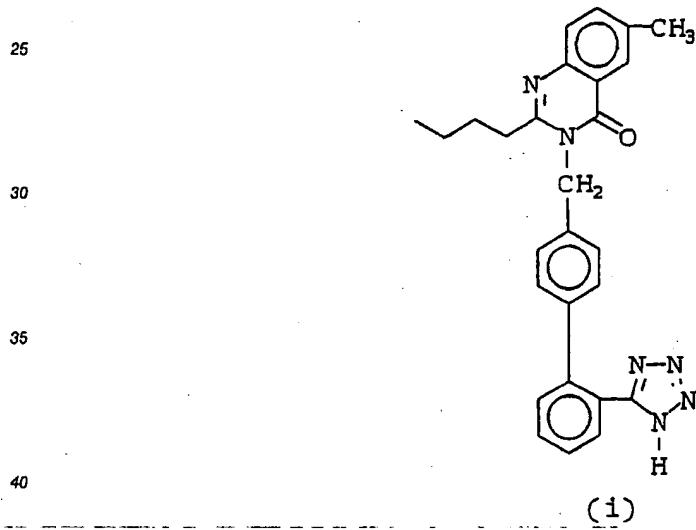
K is -C(=NR²²);
 J and L are connected together to form a 6 carbon aromatic ring substituted with R^{7a}, R^{7b}, R^{8a} and R^{8b}; and,
 the class and sub-class of this embodiment are as defined above.

Exemplifying this subclass are the following compounds:

(1) N-Methyl-2-butyl-6-(N-isopropylcarbamoyl)amino-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-imine;
 (2) N-propyl-2-butyl-6-methylsulfinyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-imine;
 (3) N-Carboxymethyl-2-butyl-6-propylsulfinyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-imine;
 (4) N-Methyl-6-acetoxymethyl-2-butyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-imine;
 (5) N-Phenyl-2-butyl-6-carboxy-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-imine;
 (6) N-Ethyl-2-butyl-6-carbomethoxy-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-imine;
 (7) N-Methyl-5-acetoxymethyl-2-butyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-imine;
 (8) N-(Pyridin-4-yl)methyl-2-butyl-5-carboxy-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-imine;
 (9) N-(2-Carboxy)ethyl-2-butyl-5-carboxymethyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-imine;
 (10) N-Methyl-2-butyl-5-carbomethoxy-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-imine;
 (11) N-Methyl-2-butyl-5-carbomethoxy-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-imine;
 (12) N-Ethyl-2-butyl-5-carbomethoxy-6-methyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-imine;
 (13) N-Butyl-2-(2-transbutenyl)-6-methylsulfinyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-imine;
 (14) N-Methyl-6-methylsulfinyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]-2-(3,3,3-trifluoropropyl)-quinazolin-4(3H)-imine;
 (15) N-Benzyl-6-methylsulfinyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]-2-(4,4,4-trifluorobutyl)-quinazolin-4-

(3H)-imine;
 (16) N-Benzyl-2-butyl-6-methyl-3-[(2'-(N-phenylsulfonyl)carboxamidobiphen-4-yl)methyl] quinazolin-4(3H)-imine;
 (17) N-(4-Chloro)phenyl-2-butyl-6-(N-isopropylcarbamoyl)amino-3-[(2'-(N-phenylsulfonyl)-carboxamidobiphen-4-yl)methyl]quinazolin-4(3H)-imine;
 5 (18) N-Methyl-2-butyl-5-carboxy-3-[(2'-(N-methylsulfonyl)carboxamidobiphen-4-yl)methyl]quinazolin-4(3H)-imine;
 (19) N-Methyl-3-[2'-(N-acetyl)sulfonamidobiphen-4-yl)methyl]-2-butyl-5-carbomethoxyquinazolin-4(3H)-imine;
 10 (20) N-Methyl-3[2'-(N-benzoyl)sulfonamidobiphen-4-yl)-methyl]-2-butyl-6-isopropylquinazolin-4(3H)-imine;
 (21) N-Methyl-2-butyl-6-isopropyl-3-[2'-(N-trifluoroacetyl)sulfonamidobiphen-4-yl)methyl]quinazolin-4(3H)-imine;
 (22) N-Methyl-2-butyl-6-isopropyl-3-[(2'-(N-pyrimidin-2-yl)sulfonamidobiphen-4-yl)methyl]quinazolin-4(3H)-imine;
 15 (23) N-Methyl-2-butyl-6-isopropyl-3-[(2'-(N-1,3,5-triazin-2-yl)sulfonamidobiphen-4-yl)methyl]quinazolin-4(3H)-imine;
 (24) N-Methyl-3-[(2'-(N-acetyl)sulfamidomethylbiphen-4-yl)methyl]-2-butyl-6-isopropylquinazolin-4(3H)-imine; and,
 (25) N-Methyl-3-[(2'-(N-acetyl)sulfamidomethylbiphen-4-yl)methyl]-2-butyl-6-isopropylquinazolin-4(3H)-imine.
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In naming compounds of Formula (I) which contain a biphenylmethyl substituent, it should be noted that the following two names for compound (i) shown below are considered to be equivalent:



45 (1) 2-Butyl-6-methyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one; or,
 (2) 2-n-Butyl-6-methyl-3-[(2'-(tetrazol-5-yl)[1,1']-biphenyl-4-yl)methyl]quinazolin-4(3H)-one.

ABBREVIATIONS USED IN SCHEMES

50 DMAP Dimethylaminopyridine
 -OTs p-toluenesulphonate
 -OTf Trifluoromethanesulfonate
 DMF Dimethylformamide
 55 DBU 1,8-Diazabicyclo[5.4.0]undecane
 FABMS Fast Atom bombardment mass spectroscopy THF Tetrahydrofuran
 DMSO Dimethylsulfoxide
 EtAc Ethyl acetate

HOAc Acetic Acid

TFA Trifluoroacetic acid.

Scheme 1 illustrates the preparation of 1,2-disubstituted quinazolin-4(1H)-ones of Formula 1 wherein J = -C(O)- and E is a single bond. An appropriately substituted anthranilonitrile is acylated using the requisite acyl chloride. The resulting amide is alkylated with sodium hydride and the appropriate alkyl halide (or pseudohalide). The resulting tertiary amide is then rearranged/cyclized with basic hydrogen peroxide¹. 2-Substituted quinazolin-4(1H)-ones 6 wherein E is a single bond and K is -C(O)- may be prepared from substituted anthranilonitriles as described in Scheme 1. The appropriately substituted anthranilonitrile is acylated using the requisite acyl chloride to give 2 then cyclized with basic hydrogen peroxide to give 6.

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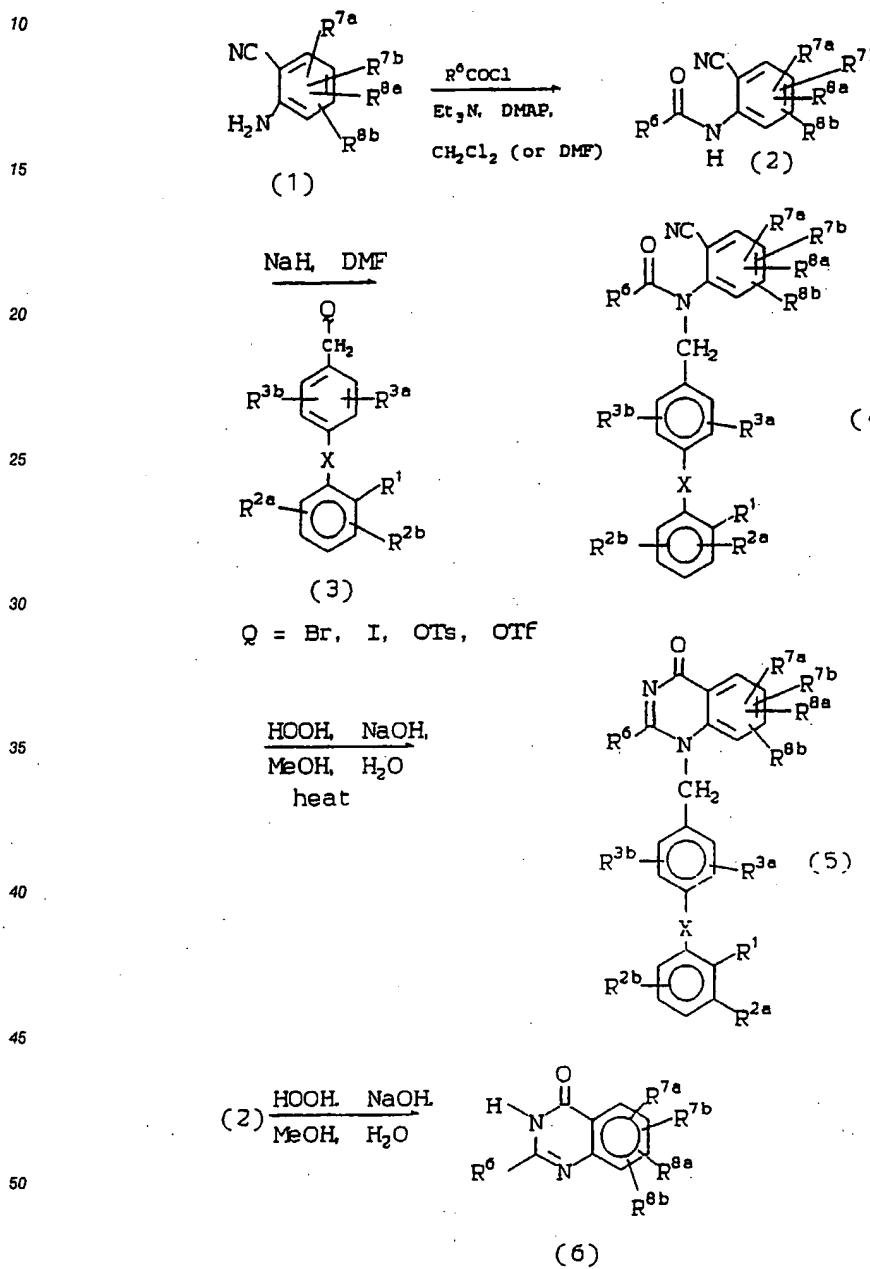
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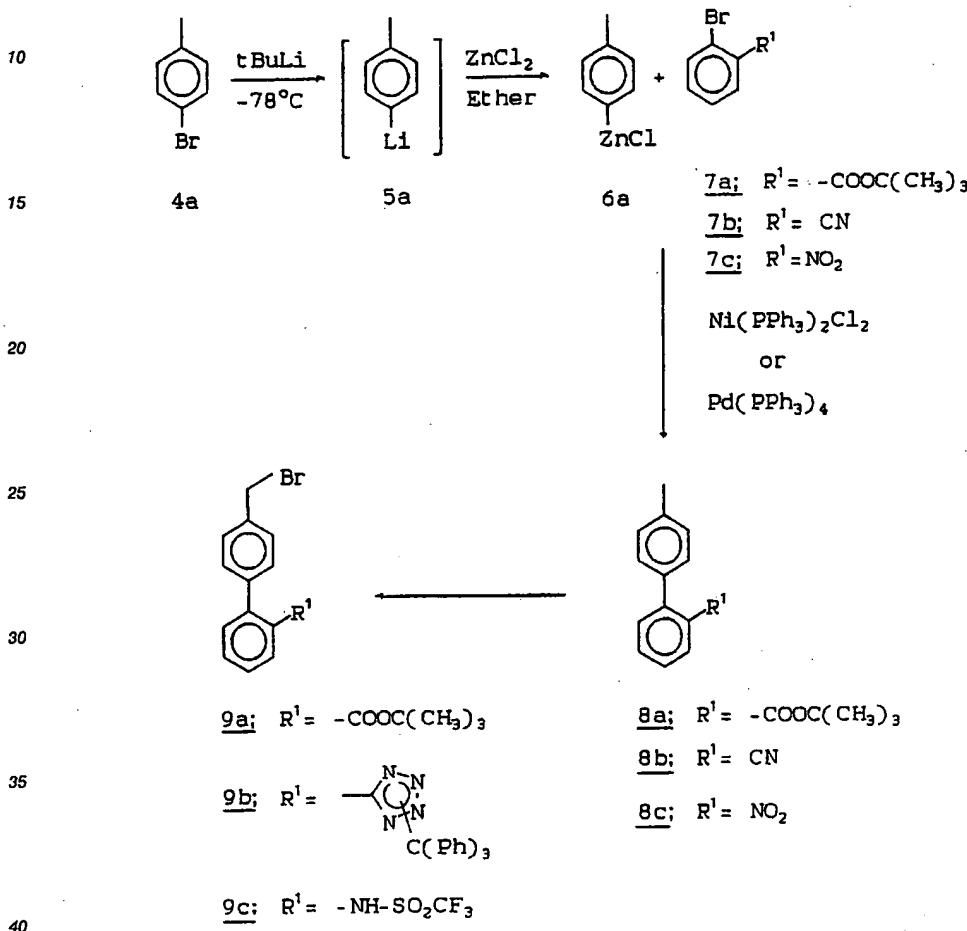
SCHEME 1

5



REACTION SCHEME 2

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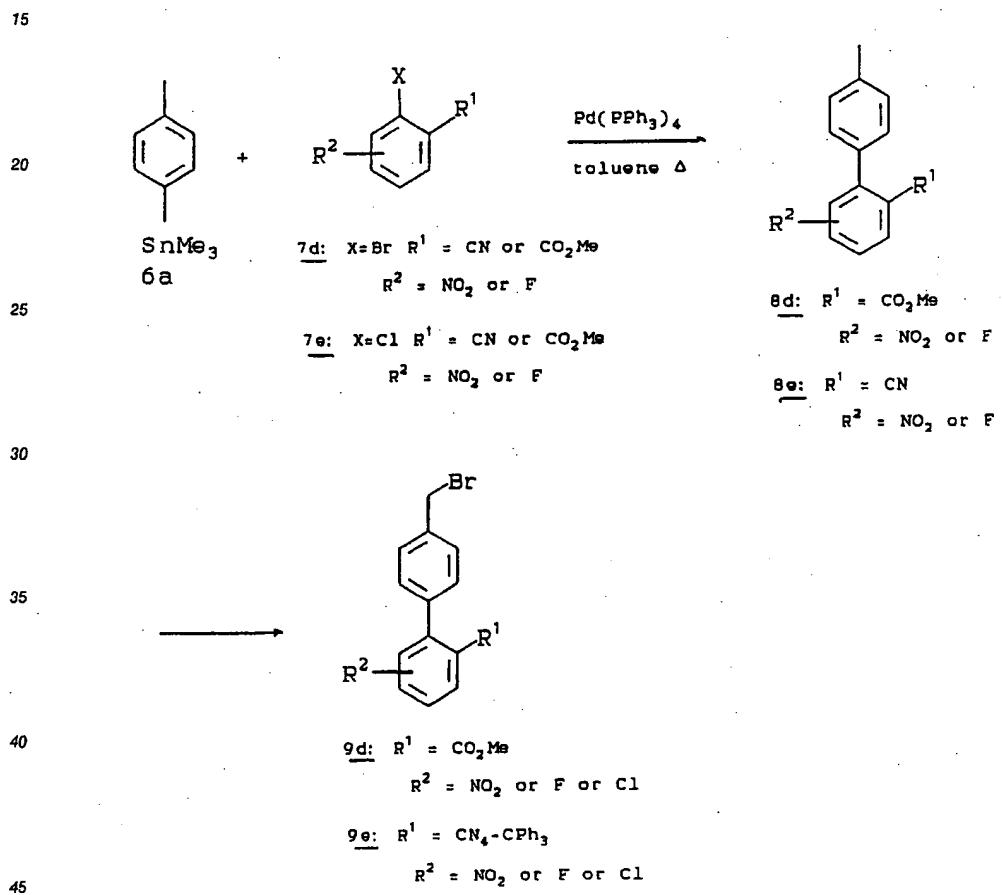


The benzyl halides (3) including the more preferred alkylating agents (9a and 9b, Reaction Scheme 2) can be prepared as described in European Patent Applications 253,310 and 291,969 and the references cited therein. However, a preferred method to prepare the biphenyl precursors 8a, 8b and 8c using Ni(O) or Pd(O) catalyzed cross-coupling reaction [E. Negishi, T. Takahashi, and A. O. King, *Org. Synthesis*, 66, 67 (1987)] is outlined in Reaction Scheme 2. As shown in Reaction Scheme 2, treatment of 4-bromotoluene (4a) with t-BuLi, followed by the addition of a solution of ZnCl₂, produces the organo-zinc compound (6a). Compound (6a) is then coupled with 7a or 7b or in the presence of Ni(PPh₃)₂Cl₂ catalyst to produce the desired biphenyl compound 8a or 8b (PPh₃ = triphenylphosphine). Similarly, 1-iodo-2-nitro-benzene (7c) is coupled with organo-zinc compound 6a in the presence of Pd(PPh₃)₄ catalyst [prepared by treating Cl₂Pd(PPh₃)₂ with (i-Bu)₂AlH (2 equiv.)] to give the biphenyl compound 8c. These precursors, 8a, and 8b and 8c, are then transformed into halomethylbiphenyl derivatives 9a, 9b and 9c, respectively, according to procedures described in European Patent Applications 253,310 and 291,969.

When there is additional substitution on the second phenyl ring (R^{2a}, R^{2b} ≠ hydrogen) the preferred method to prepare the biphenyl precursors 8d and 8e, using the Pd(O) catalyzed cross-coupling reaction [J. K. Stille, *Angew. Chem. Int. Ed. Engl.*, 25, 508 (1986)], is outlined in reaction Scheme 2a. As shown in reaction Scheme 2a, p-tolyltrimethyltin (6a) is coupled with 7d or 7e in refluxing toluene in the presence of 5 mole % of Pd(PPh₃)₄ to produce the desired biphenyl compounds 8d and 8e. Table I illustrates the

synthetic utility of this protocol. Compounds 8d ($R^2 = NO_2$) and 8e ($R^2 = NO_2$) could be converted to their respective chlorides by catalytic hydrogenation, diazotization and treatment with copper (I) chloride. The biphenyl fluorides which could not be obtained by direct coupling to a fluoro arylbromide were prepared from 8d ($R^2 = NO_2$) and 8e ($R^2 = NO_2$) via reduction, formation of the diazonium tetrafluoroborate salt and thermal decomposition. These precursors 8d ($R^2 = NO_2$ or F or Cl) and ($R^2 = NO_2$ or F or Cl) are then transformed into the halomethyl biphenyl derivatives 9d and 9e, respectively according to the procedures described in European Patent Applications 253,310 and 292,969.

10 REACTION SCHEME 2a



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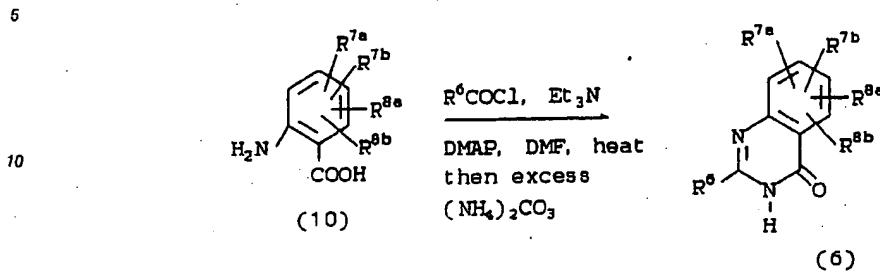
Biphenyl Synthesis Table I

X	R ^a	R ^b	R ^c	R ^d	Product (R ^a)	RF (solvent)	Yield
Br	CO ₂ Me	NO ₂	H	H	<u>8d</u> (3'-nitro)	0.35(15:1 Hex/EtOAc)	71%
Br	CN	H	NO ₂	H	<u>8e</u> (4'-nitro)	0.62(2x 6:1 Hex/EtOAc)	74%
Br	CO ₂ Me	H	F	H	<u>8d</u> (4'-fluoro)	0.43(15:1 Hex/EtOAc)	83%
C1	CO ₂ Me	H	H	NO ₂	<u>8d</u> (5'-nitro)	0.22(15:1 Hex/EtOAc)	70%
Br	CO ₂ Me	H	H	NO ₂	<u>8d</u> (6'-nitro)	0.24(15:1 Hex/EtOAc)	79%
Br	CN	H	F	H	<u>8e</u> (4'-fluoro)	0.44(15:1 Hex/EtOAc)	64%
C1	CN	H	H	F	<u>8e</u> (5'-fluoro)	0.40(15:1 Hex/EtOAc)	62%

50 Scheme 3 shows an alternate preparation of 2-substituted quinazolin-4(3H)-ones (6) starting with the corresponding anthranilic acid. The appropriately substituted anthranilic acid (10) is treated with two equivalents of the requisite acyl chloride in DMF with triethylamine and DMAP at 0 °C. This is then heated to 110 °C for two hours after which time excess ammonium carbonate is added.²

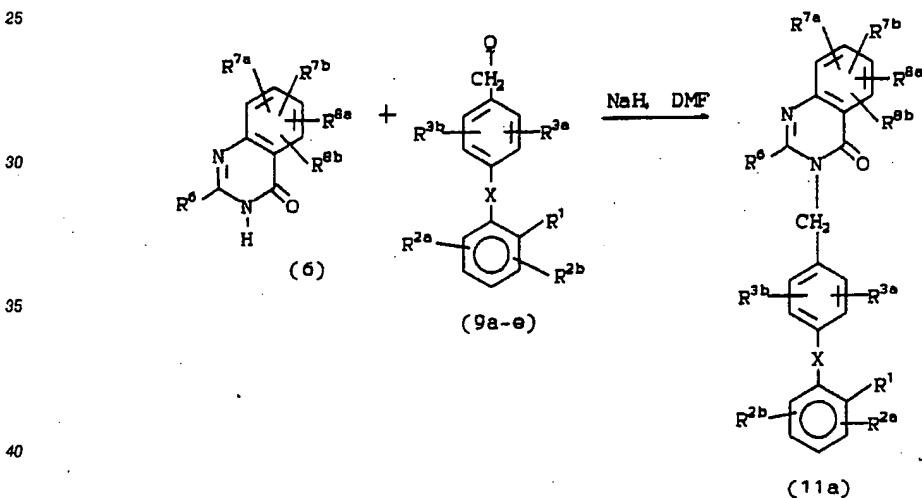
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SCHEME 3



Scheme 4 illustrates the general preparation of 2,3-disubstituted quinazolin-4(3H)-ones (11a) of Formula (I) wherein E is a single bond and K is $-\text{C}(\text{O})-$. An appropriately substituted 2-substituted quinazolin-4(1H)-one (6) (see Scheme 1 or Scheme 3) is alkylated using sodium hydride and the appropriate alkyl halide (or pseudohalide). This reaction sometimes gives some O-alkylated product, generally less than 20% of the isolated reaction products.

SCHEME 4



Schemes 5, 6, and 7 provide an alternate route to compounds of Formula (1) (11b) wherein E is a single bond, K is $-\text{C}(\text{O})-$, and r is 1 or 2.

Two methods for preparing 3,1,4-benzoxazones (10) are illustrated in Scheme 5. Substituted anthranilic acids (10) may be acylated and cyclized by heating them in DMF with an acyl chloride, triethylamine and DMAP.³ Alternatively, they may also be prepared by heating an appropriately substituted anthranil (13) with an acyl chloride in pyridine.⁴

The necessary alkyl amine may then be prepared from the alkyl halide (or pseudohalide) using the standard literature procedures (Scheme 6).⁵ The amine where r = 2 may be prepared from (9a-e) using procedures known to those skilled in the art where appropriate protecting groups are used for R^1 , R^{2a} , R^{2b} , R^{3a} and R^{3b} . Then, the amine and the 3,1,4-benzoxazone are heated together to give the desired 2,3-disubstituted quinazolinone (11b) (Scheme 7).

SCHEME 5

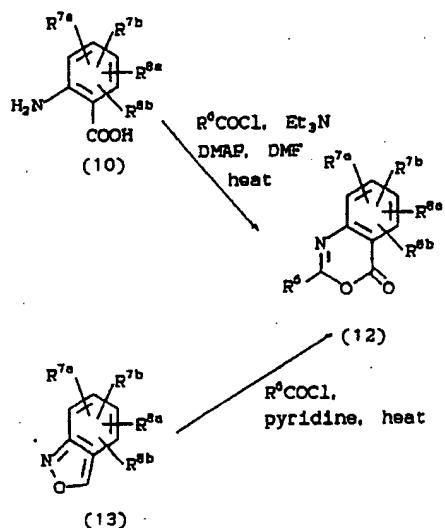
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SCHEME 6

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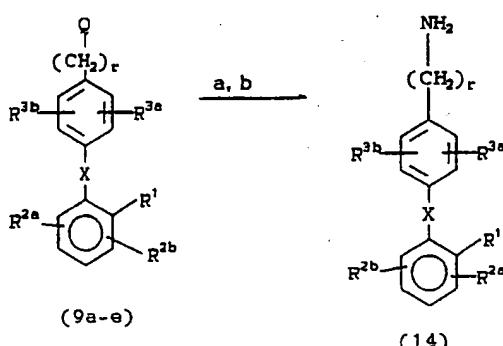
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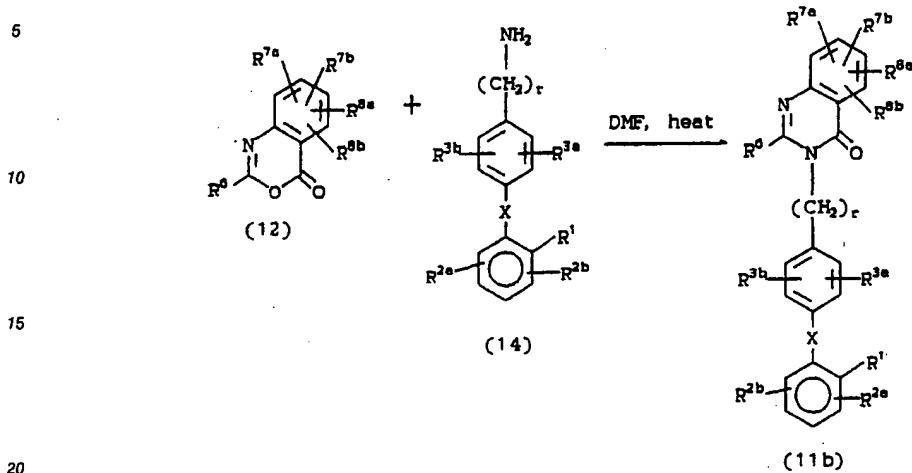
for $r = 1$:

- a) LiN_3/DMSO
- b) $\text{P}(\text{Ph})_3, \text{H}_2\text{O}$

for $r = 2$:

- a) $\text{Na}^+\text{CH}_2\text{NO}_2, \text{DMF}$
- b) $\text{H}_2, 10\% \text{Pd/C}$

SCHEME 7



Substituted 2-alkylthioquinazolin-4(3H)-ones wherein K is -C(O)- and E is -S- (15) may be prepared from their corresponding substituted anthranilic acids as shown in Scheme 8. The amine (14) from Scheme 6 can be converted to its isothiocyanate (16) upon treatment with thiophosgene. This may then be reacted with an appropriately substituted anthranilic acid to give the desired 3-alkyl-2-mercaptop-quinazolin-4(3H)-one.(17)⁶ A second alkylation of the mercapto group then gives the desired 2-alkylthio-3-alkylquinazolin-4(3H)-one. (15)⁷

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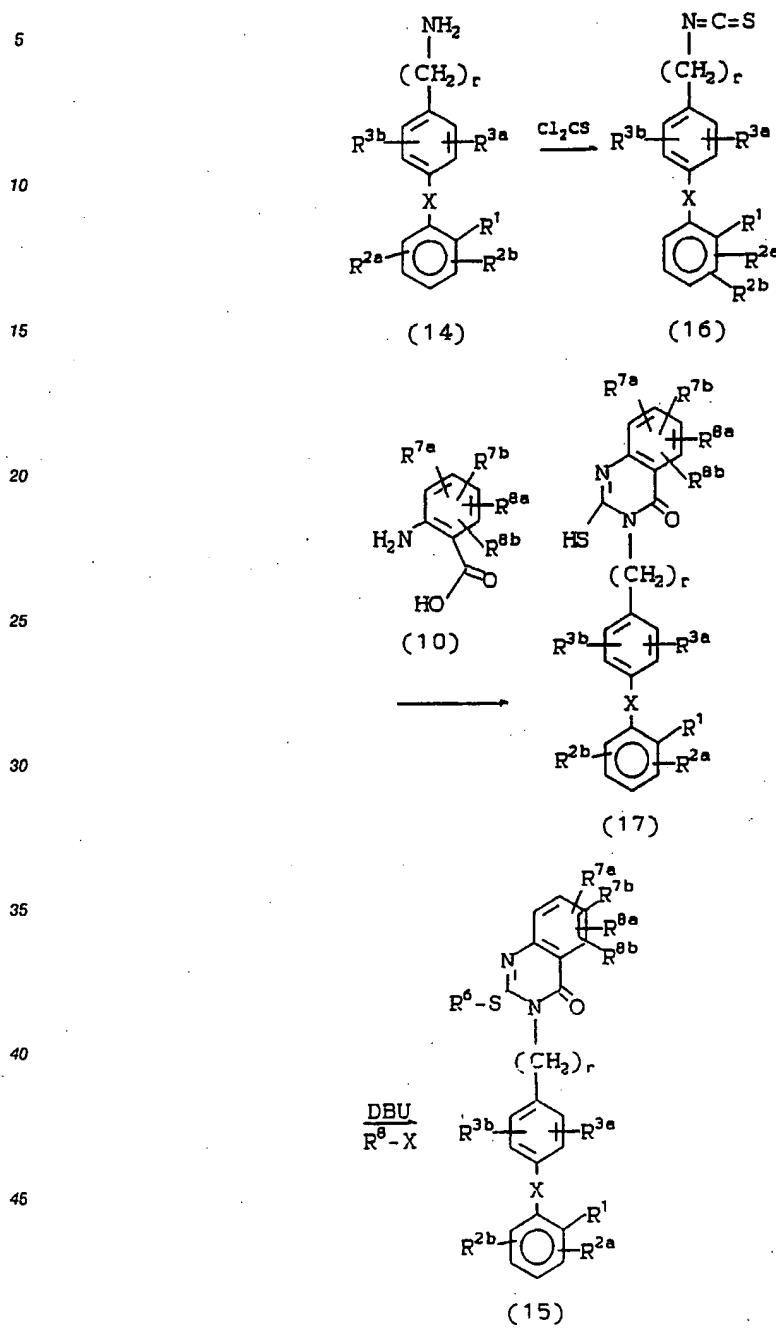
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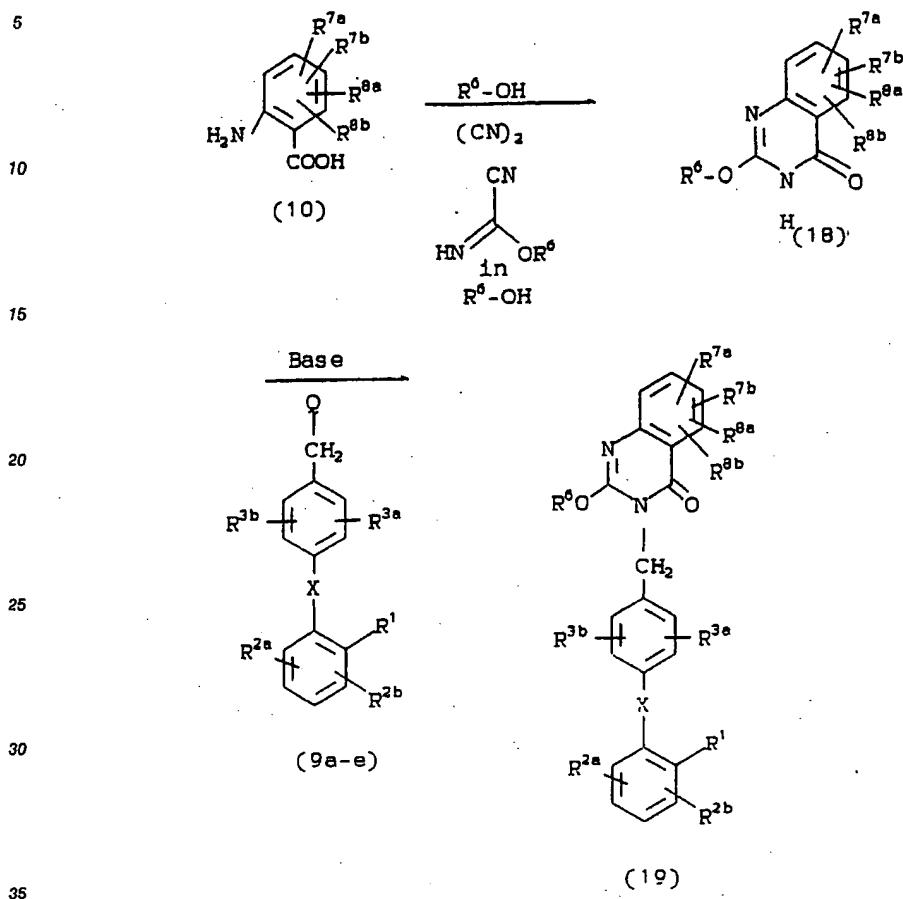
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SCHEME 8



Similarly, 2-alkoxyquinazolin-4(3H)-ones wherein K is -C(O)- and E is -O- may be prepared from their corresponding substituted anthranilic acids as shown in Scheme 9.⁸ Alkylation with the appropriate alkyl halide 9a-e according to the methods developed by Lange and Sheibley⁹ then gives the final product 19.

SCHEME 9



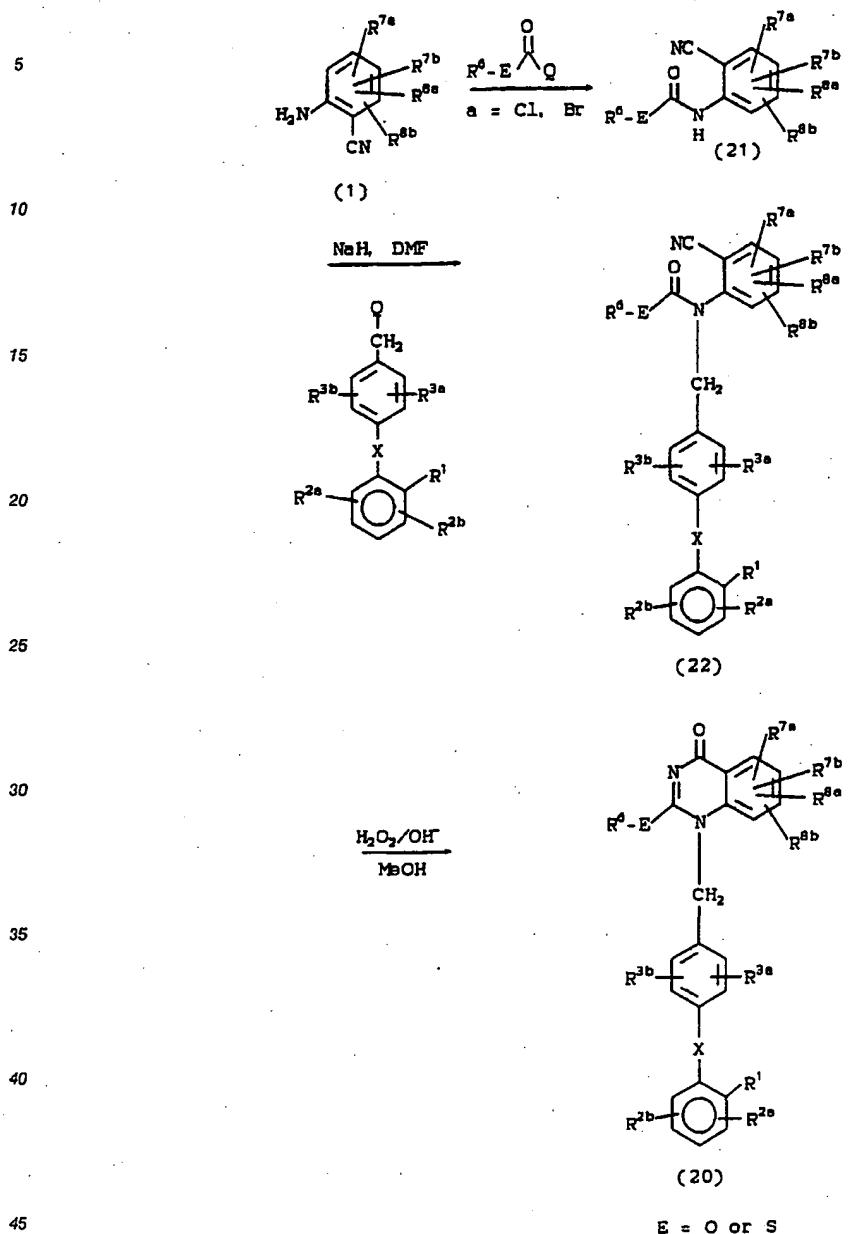
Scheme 10 illustrates a route to the isomeric 1,2-disubstituted quinazolin-4(1H)-ones (20) wherein J is -C(O)- and where E is S or O. An anthranilonitrile 1 is acylated with an alkyl haloformate or an alkylthiol haloformate to give 21.¹⁰ This may then be deprotonated and alkylated with the appropriate alkyl halide to give the intermediate carbamate nitrile 22.¹¹ Conversion of the intermediate then occurs when the material is treated with basic hydrogen peroxide to yield the desired product 20.

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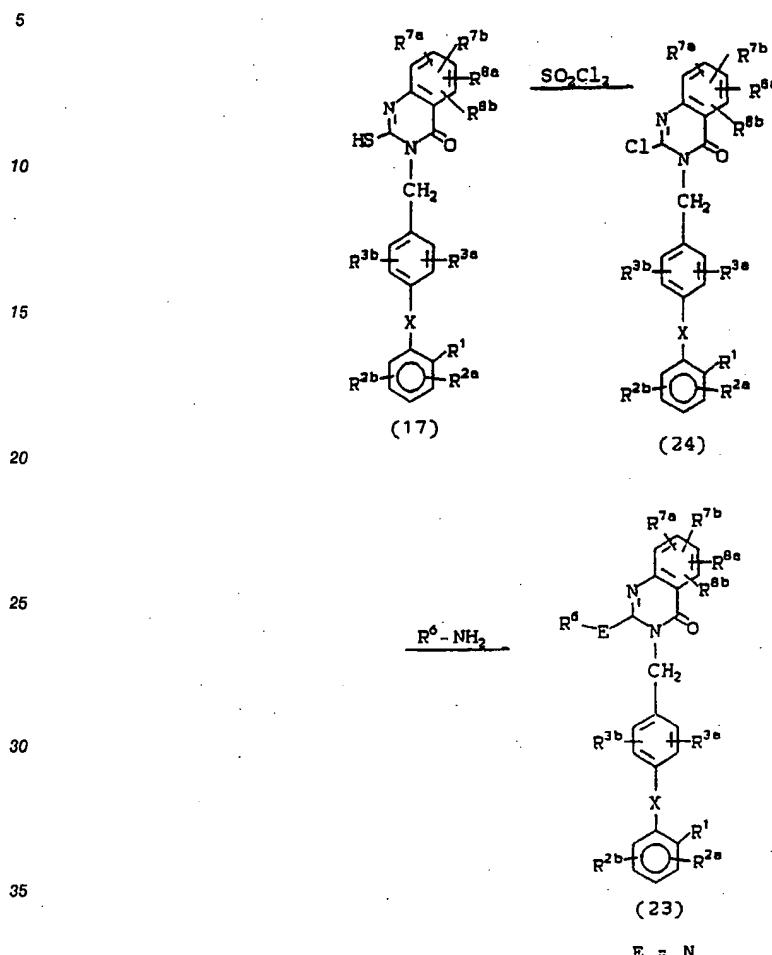
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SCHEME 10



Scheme 11 illustrates the method by which a 2-amino-3-alkylquinazolinone 23 can be made. The 2-50 mercaptoquinazolinone (17) shown in Scheme 8 can be treated with sulfonyl chloride to give the corresponding 2-chloroquinazolinone 24.¹² Displacement of the chloride with an R⁶ amine then gives 23 with E = NH.¹³

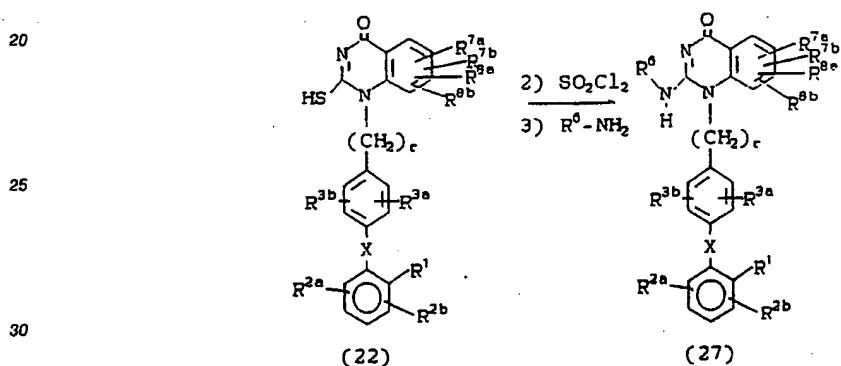
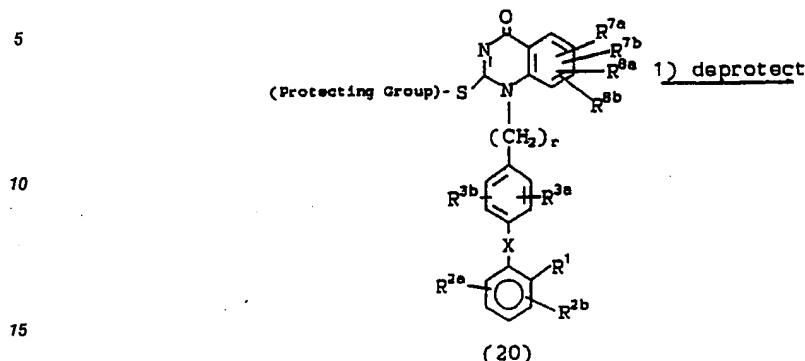
SCHEME 11



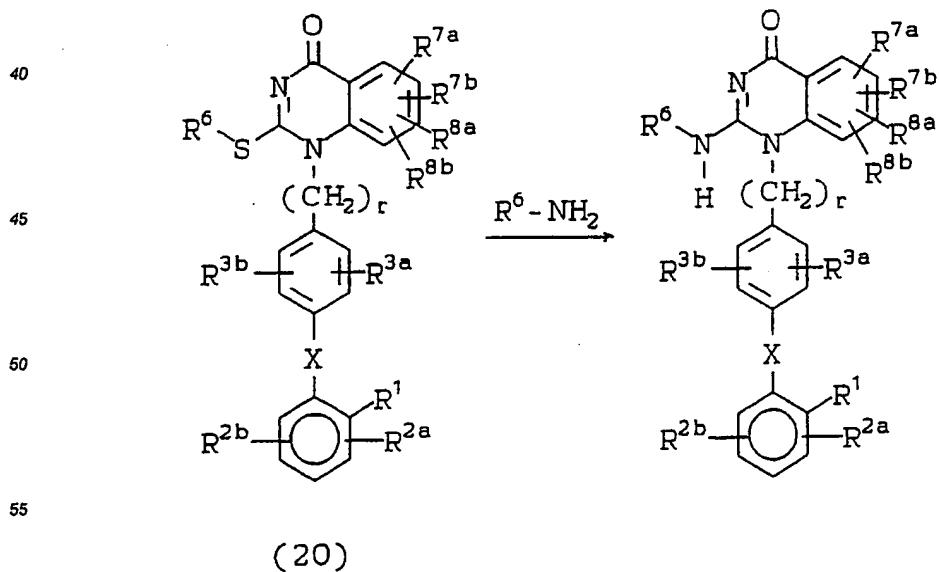
40 Scheme 12 illustrates the method by which a 2-amino-1-alkylquinazolinone 24 can be made. The products from Scheme 10 where E is sulfur (20) can be used as a synthetic intermediate if the initial R^6 is a protecting group such as benzyl or t-butyl.¹⁴ Deprotection and subjection of the resulting 2-mercapto-1-alkyl-quinazolinone to the same conditions used in Scheme 11 will result in the formation of the desired 2-amino-1-alkylquinazolinone. Alternatively, the sulfide may be displaced directly by an R^6 amine as shown in

45 Scheme 13 (R^6 -S- and R^6 -NH₂ may or may not have the same R^6).

SCHEME 12



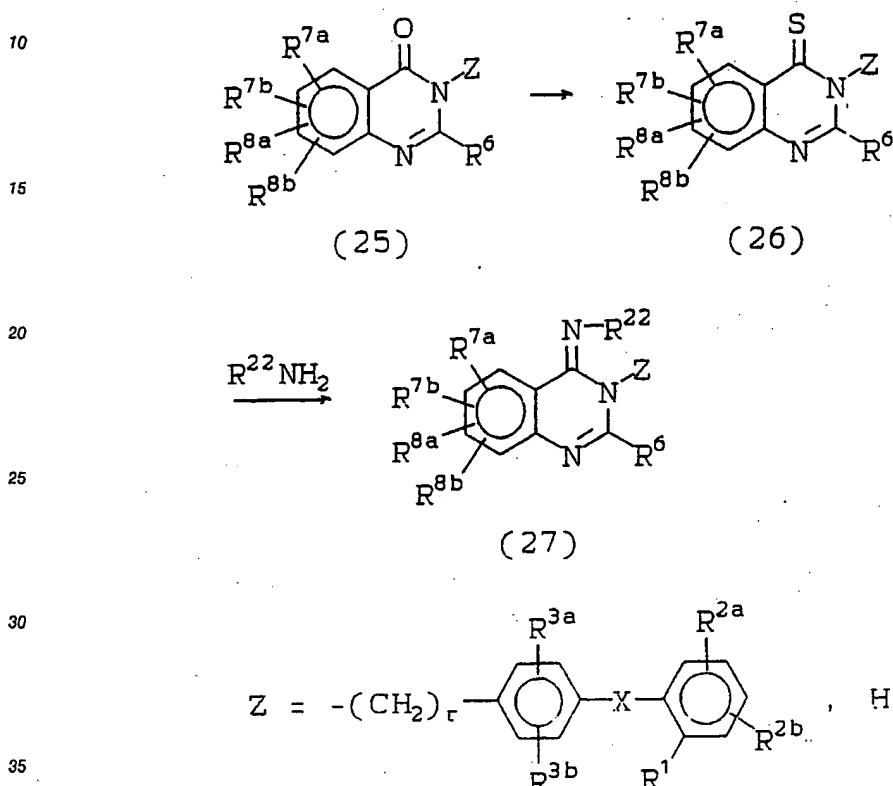
SCHEME 13



Scheme 14 illustrates the method by which a quinazolin-4(3H)-imine 27 may be prepared. A 3-substituted or unsubstituted quinazolin-4(3H)-one can be converted to a quinazolin-4(3H)-thione 26 by the action of Lewesson's reagent. Addition of amine and heating will result in the formation of an imine 27 as shown.

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SCHEME 14



Compounds of formula I where R^1 is $-\text{CONHSO}_2R^{23}$ (where R^{23} = alkyl, aryl or heteroaryl) may be prepared from the corresponding carboxylic acid derivatives (28) as outlined in Scheme 15. The carboxylic acid (28), obtained as described in Scheme 4, can be converted into the corresponding acid chloride by treatment with refluxing thionyl chloride or preferably with oxalylchloride and a catalytic amount of dimethylformamide at low temperature [A.W. Burgstahler, L.O. Weigel, and C.G. Shaefer- *Synthesis*, 767, (1976)]. The acid chloride then can be treated with the alkali metal salt of $R^{23}\text{SO}_2\text{NH}_2$ to form the desired acylsulfonamide 29. Alternatively, these acylsulfonamides may be also prepared from the carboxylic acids using N,N-diphenylcarbamoyl anhydride intermediates [F.J. Brown et al, European Patent Application, EP 199543; K.L. Shepard and W. Halzenko- *J. Het. Chem.*, 16, 321 (1979)]. Preferably the carboxylic acids can be converted into acyl-imidazole intermediates, which then can be treated with an appropriate aryl or alkylsulfonamide and diazabicycloundecane (DBU) to give the desired acylsulfonamide 29 [J.T. Drummond and G. Johnson, *Tet. Lett.*, 29, 1653 (1988)].

Compounds of formula I where R^1 is $\text{SO}_2\text{NHCOR}^{23}$ may be prepared as outlined in Scheme 16. The nitro compound 8c (prepared as described in Scheme 2) can be reduced to the corresponding amino compound and converted into aromatic diazonium chloride salt, which then can be reacted with sulfur-dioxide in the presence of a copper (II) salt to form the corresponding arylsulfonyl chloride 30 [H. Meerwein, G. Dittmar, R. Gollner, K. Hafner, F. Mensch and O. Steifort, *Chem. Ber.*, 90, 841 (1957); A.J. Prinsen and H. Cerfontain, *Recueil*, 84, 24 (1965); E.E. Gilbert, *Synthesis*, 3 (1969) and references cited therein]. The sulfonyl chloride can be reacted with ammonia in aqueous solution or in an inert organic solvent [F.H. Bergheim and W. Baker, *J. Amer. Chem. Soc.*, 66, (1944), 1459], or with dry powdered ammonium

carbonate, [E.H. Huntress and J.S. Autenrieth, J. Amer. Chem. Soc., 63 (1941), 3446; E.H. Huntress and F.H. Carten, J. Amer. Chem. Soc., 62, (1940), 511] to form the sulfonamide 31. The benzylbromide 33 may be prepared from the sulfonamide 31 as outlined in Scheme 16, and then can be reacted with an alkali metal salt of an appropriate heterocyclic compound to form the key sulfonamide 34. The sulfonamide 34 may be also prepared from the aromatic sulfonyl chloride 39, which may be prepared from the aryl amine 38 as outlined in Scheme 17. The acylation of 34 with appropriate acyl chlorides (or acyl-imidazoles or other acylating agents) may produce the desired acylsulfonamides 35.

The compounds bearing R¹ as -SO₂NHR²³ (where R²³ is heteroaryl) may be prepared by reacting the aromatic sulfonyl chloride 39 with appropriate heteroaryl amines as outlined in Scheme 17. The sulfonyl chloride 39 may be the preferred intermediate for the synthesis of this class of compounds. The aromatic sulfonyl chlorides may also be prepared by reacting the sodium salt of aromatic sulfonic acids with PCls or POCl₃ [C.M. Suter, The Organic Chemistry of Sulfur, John Wiley & Sons, 459, (1944)]. The aromatic sulfonic acid precursors may be prepared by chlorosulfonation of the aromatic ring with chlorosulfonic acid [E.H. Huntress and F.H. Carten, J. Amer. Chem. Soc., 62, 511 (1940)].

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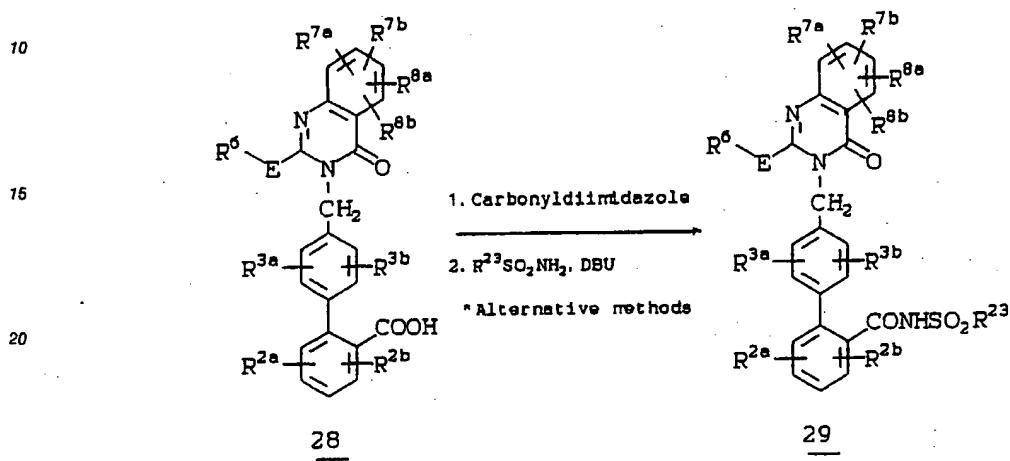
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SCHEME 15

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*Alternative Methods:

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a) (i) SOCl_2 , reflux
 (ii) $\text{R}^{23}\text{SO}_2\text{NH}^-\text{M}^+$ (where M is Na or Li)

b) (i) $(\text{COCl})_2$ -DMF, -20°C
 (ii) $\text{R}^{23}\text{SO}_2\text{NH}^-\text{M}^+$

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c) (i) $\text{N}(\text{N,N-Diphenylcarbamoyl})\text{pyridinium chloride}/$
 Aq. NaOH
 (ii) $\text{R}^{23}\text{SO}_2\text{NH}^-\text{M}^+$.

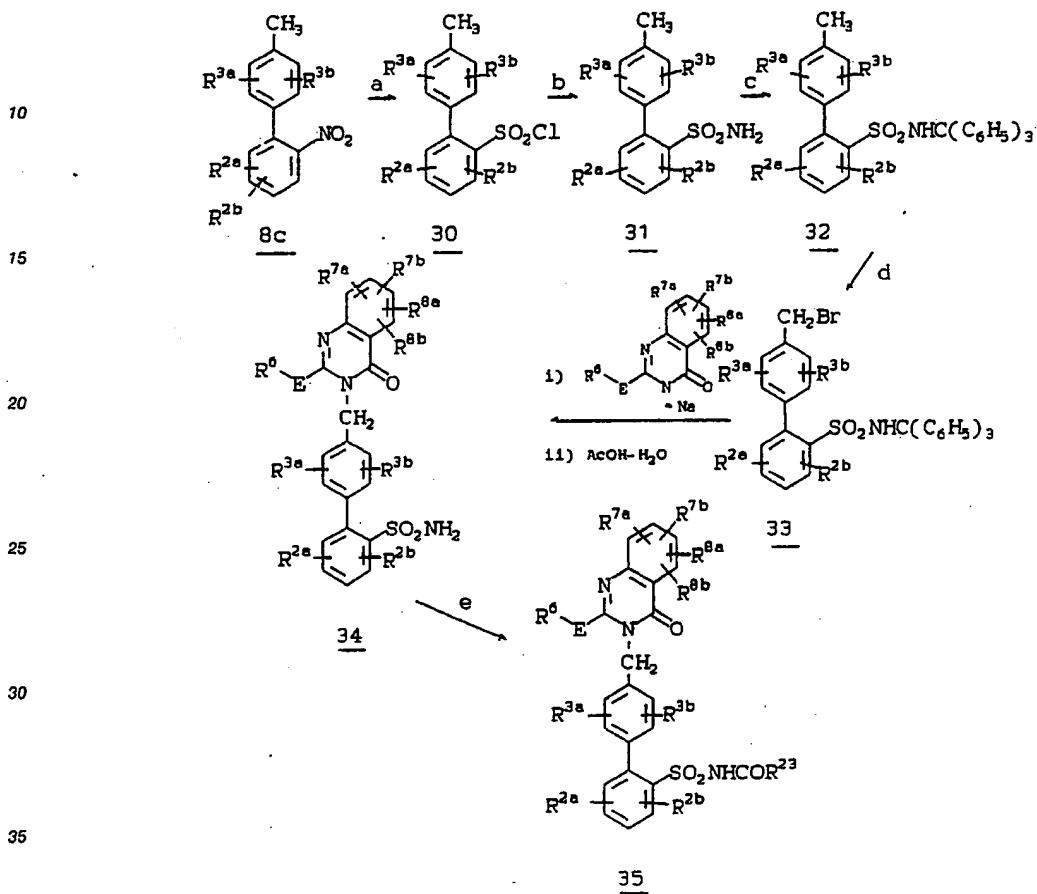
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SCHEME 16

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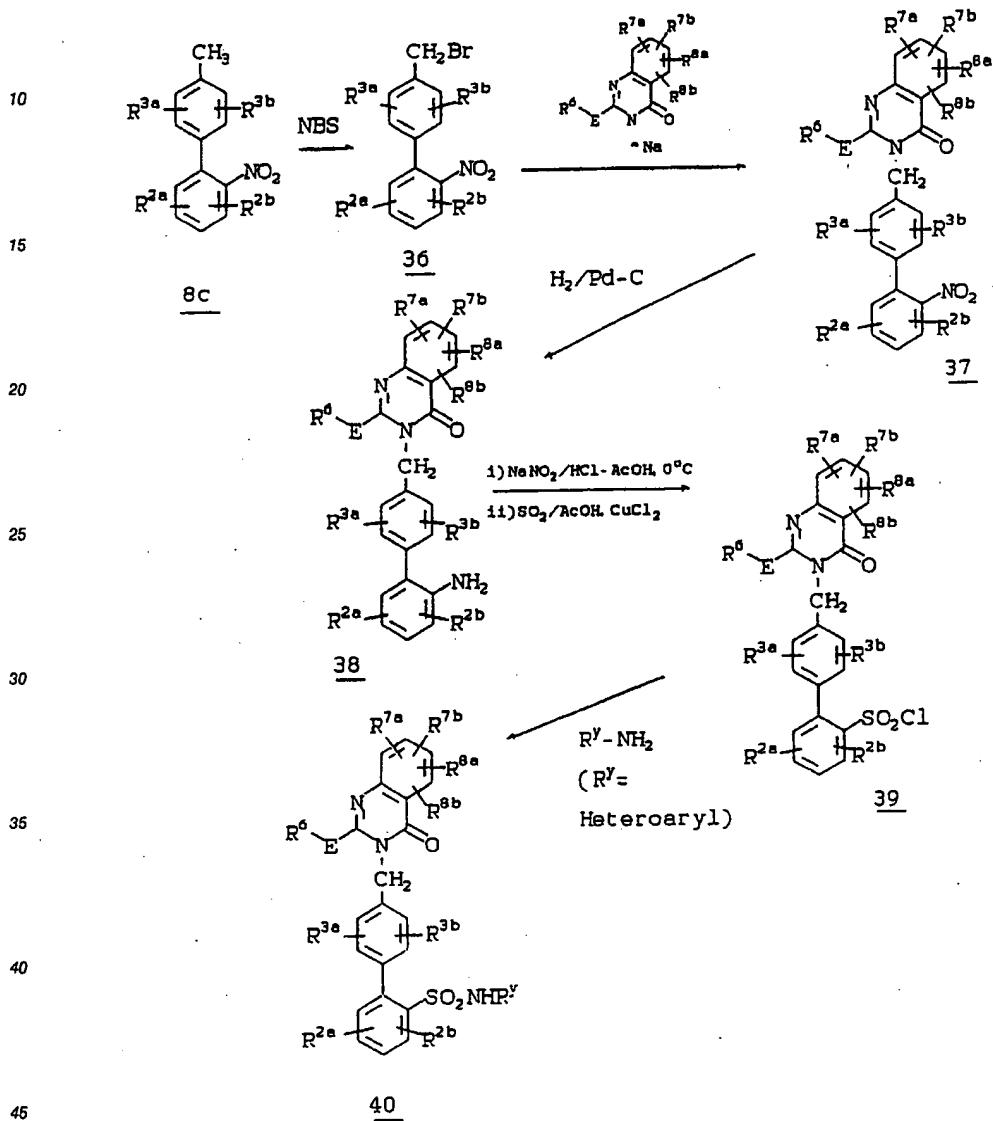
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45 a. (i) $\text{H}_2/\text{Pd-C}$,
(ii) $\text{NaNO}_2\text{-HCl}$,
(iii) SO_2 , AcOH , CuCl_2
b. NH_3 or $(\text{NH}_4)_2\text{CO}_3$
c. $(\text{C}_6\text{H}_5)_3\text{CCl}$, Et_3N , CH_2Cl_2 , 25°C
d. N-Bromosuccinimide
50 e. R^{23}COCl or $\text{R}^{23}\text{CO-Im}$ or other acylating agents.

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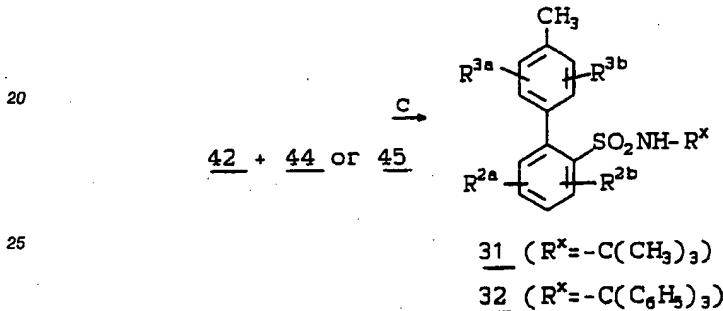
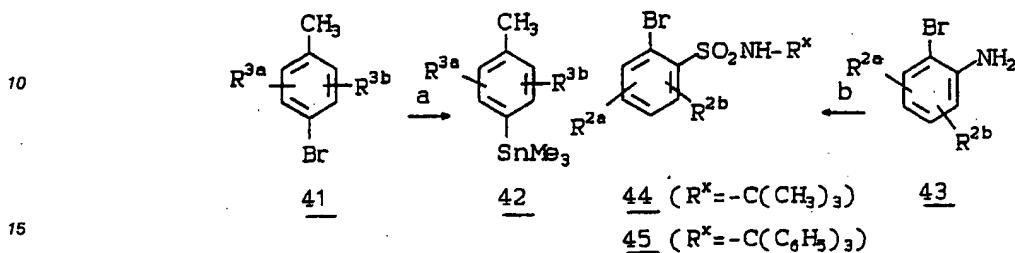
SCHEME 17

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SCHEME 18

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a. (i) $t\text{-BuLi/ether, } -78^\circ\text{C}$
 35 (ii) Me_3SnCl

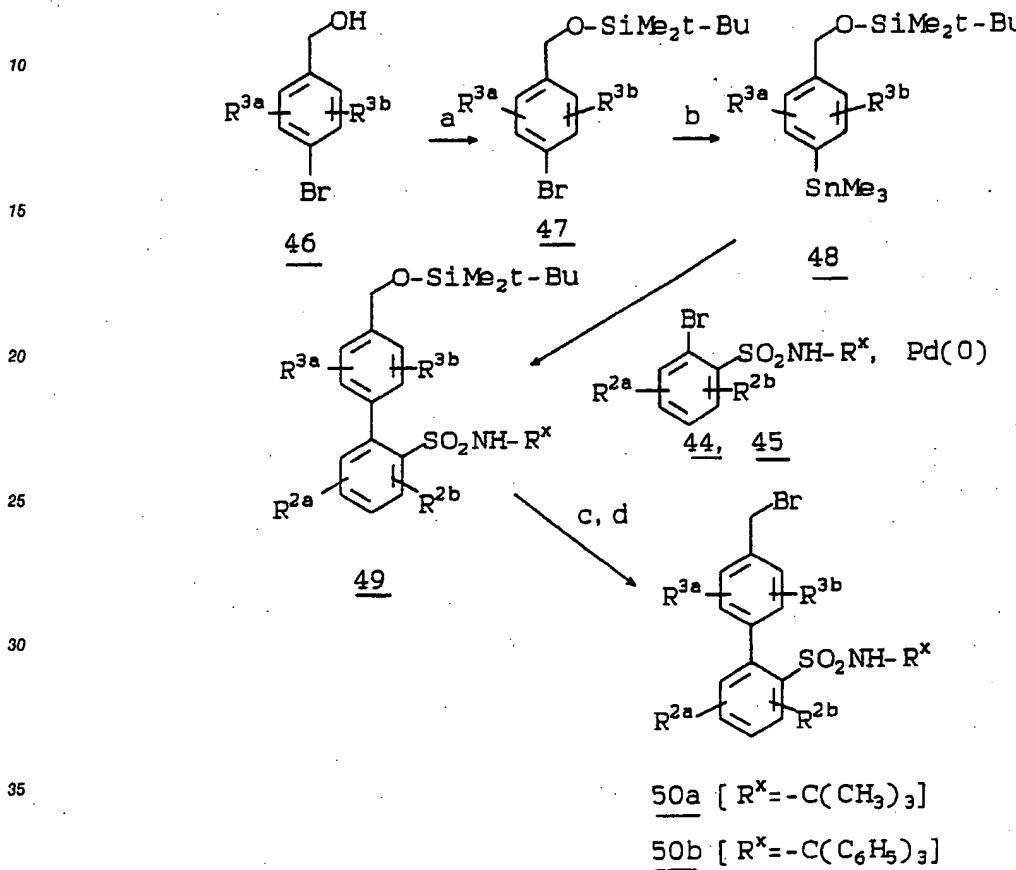
b. (i) $NaNO_2/HCl$
 (ii) $SO_2, CuCl_2$
 40 (iii) R^X-NH_2

c. $Pd(PPh_3)_4$, Toluene, Reflux or $(PPh_3)_2PdCl_2$, DMF,
 45 90°C

45 The biaryl sulfonamides 31 and 32 (described in Scheme 16) can be prepared alternatively using palladium(0) catalyzed cross-coupling reactions of appropriate aryl-organotin precursors [J.K. Stille, *Tet. Pure Appl. Chem.*, 57, 1771 (1985); T.R. Baily, *Lett.*, 27, 4407 (1986); D.A. Widdowson and Y.Z. Zhang, *Tetrahedron*, 42, 2111 (1986)], as outlined in Scheme 18. The organotin compound 42 [S.M. Moerlein, *J. Organometallic Chem.*, 319, 29 (1987)], obtained from the aromatic precursor 41, may be coupled with 50 aryl sulfonamide 44 and 45 using $Pd(PPh_3)_4$ or $(PPh_3)_2PdCl_2$ as catalysts to give biaryl sulfonamide 31a and 32 respectively. Similarly, the benzyl bromides 50a and 50b may be alternatively prepared from the appropriate organotin precursor 48 using the Pd(0) catalyzed cross-coupling reaction as outlined in Scheme 55 19.

SCHEME 19

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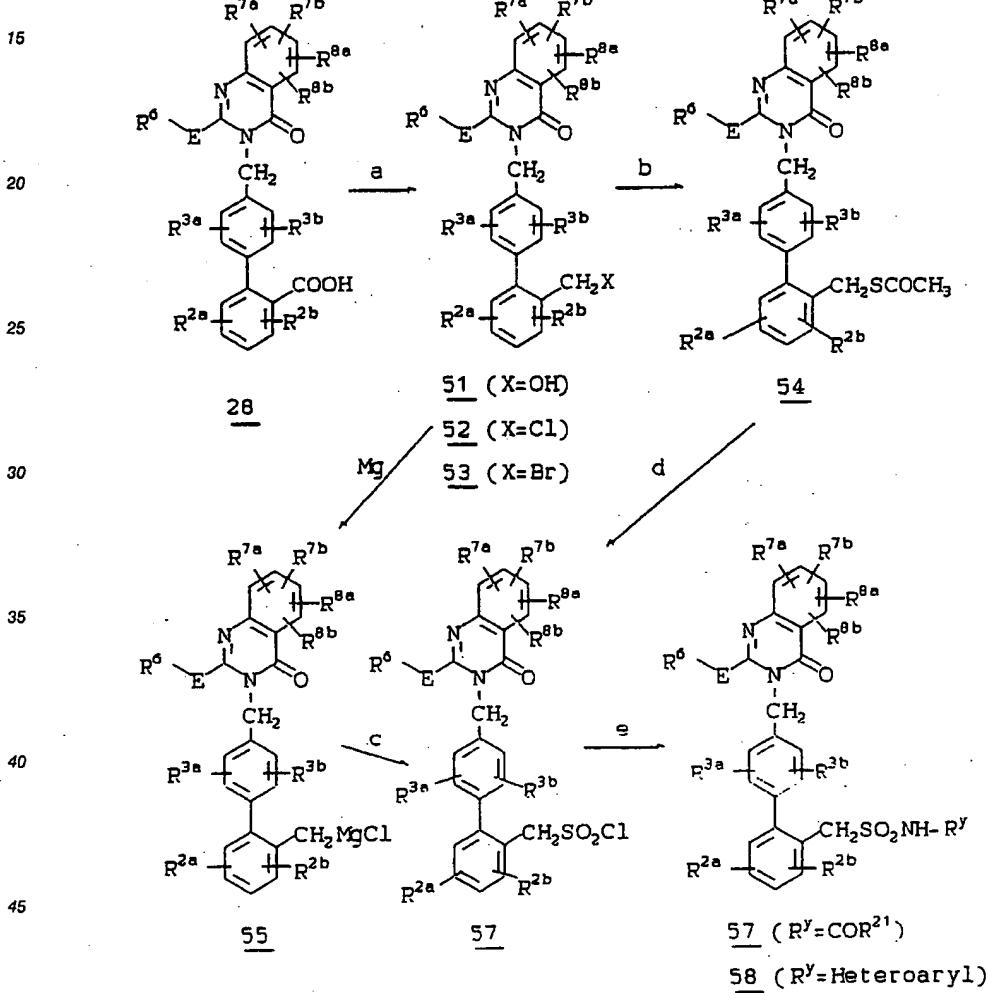
a. $t\text{-BuMe}_2\text{Si-Cl/Imidazole, DMF}$
 b. $t\text{-BuLi, } -78^\circ\text{C, Me}_3\text{SnCl}$
 c. Tetrabutylammonium fluoride
 d. $\text{CBr}_4/\text{Ph}_3\text{P}$.

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SCHEME 20

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SCHEME 20 (CONT'D)

- 5 a. (i) $\text{EtOCOCl/Et}_3\text{N}$, THF, 0°C
 (ii) NaBH_4
 (iii) CCl_4 or $\text{CBr}_4/\text{PPh}_3$
- 10 b. AcSK
- c. SO_2Cl_2
- d. Cl_2 , AcOH , H_2O or,
 (i) SO_2Cl_2
 (ii) oxidation
- 15 e. R^yNH_2 or,
 (i) NH_3
 (ii) Acylation.

20 The compounds bearing $\text{R}^1 = -\text{CH}_2\text{SO}_2\text{NHCOR}^{23}$ and $-\text{CH}_2\text{SO}_2\text{NHR}^{23}$ may be prepared as outlined in Scheme 20. The key precursor aryl-methanesulfonyl chloride 56 may be prepared either from the reaction of arylmethylmagnesium chloride 55, obtained from the corresponding benzyl chloride 52, with sulfonyl chloride [S.N. Bhattacharya, C. Earborn and D.P.M. Walton, *J. Chem. Soc. C*, 1265 (1968)], or by oxidation of the aryl-methylthioacetate 54 (prepared from the benzyl bromide 53 with chlorine in presence of trace amount of water [Bagnay and Dransch, *Chem. Ber.*, 93, 784 (1960)]). Alternatively, the aryl-methylthioacetate 54 can be oxidized with sulfonyl chloride in presence of acetic anhydride to form arylmethylsulfinyl chloride [S. Thea and G. Cevasco, *Tetra. Lett.*, 28, 5193 (1987)], which can be further oxidized with appropriate oxidizing agents to give the sulfonyl chloride 56. The compounds 57 and 58 can be obtained by reacting the sulfonyl chloride 56 with appropriate amines.

25 Compounds where $\text{R}^1 = -\text{NHSO}_2\text{NHR}^{23}$ may be prepared by the reaction of appropriate primary amines with the sulfamide 60 [S.D. McDermott and W.J. Spillane, *Synthesis*, 192 (1983)], as described in Scheme 21. The compound 60 may be obtained from the corresponding *N*-t-butylsulfamide 59 after 30 treatment with anhydrous trifluoroacetic acid [J.D. Catt and W.L. Matier, *J. Org. Chem.*, 566 (1974)], which may be prepared by the reaction of the aromatic amine 38 with t-butylsulfamoyl chloride [W.L. Matier, W.T. Comer and D. Deitchman, *J. Med. Chem.*, 15, 538 (1972)].

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SCHEME 21

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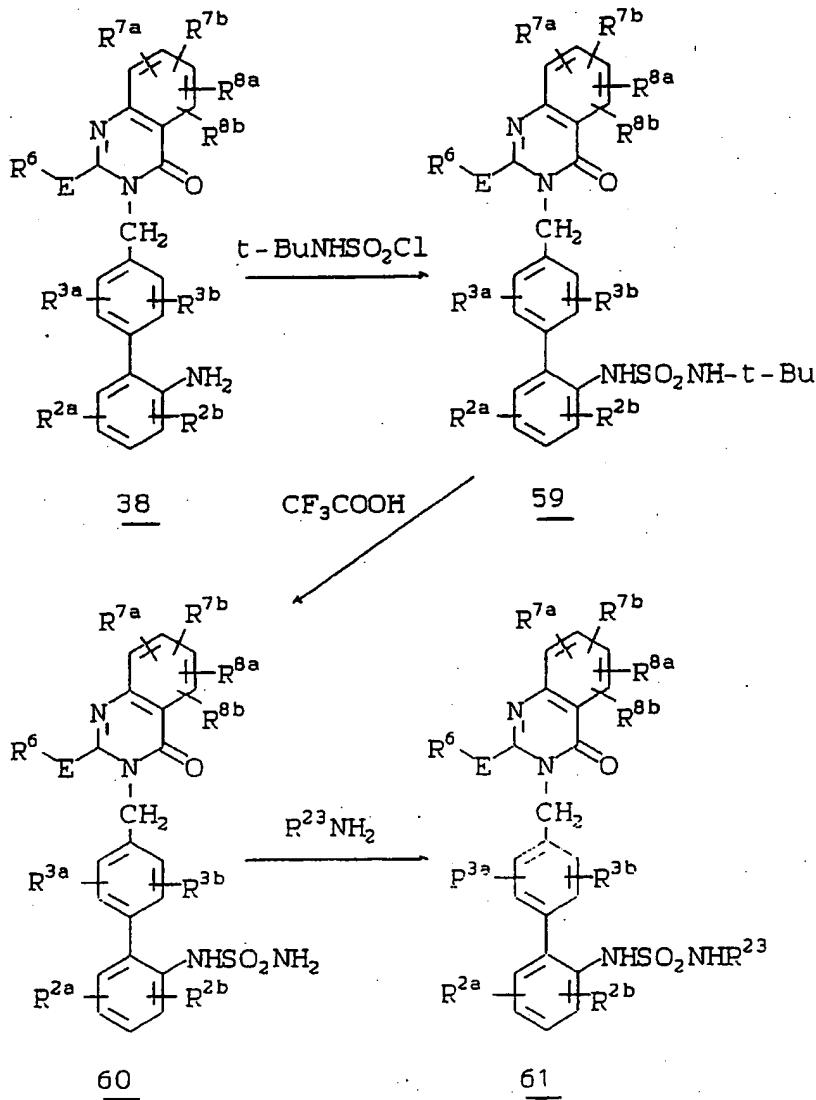
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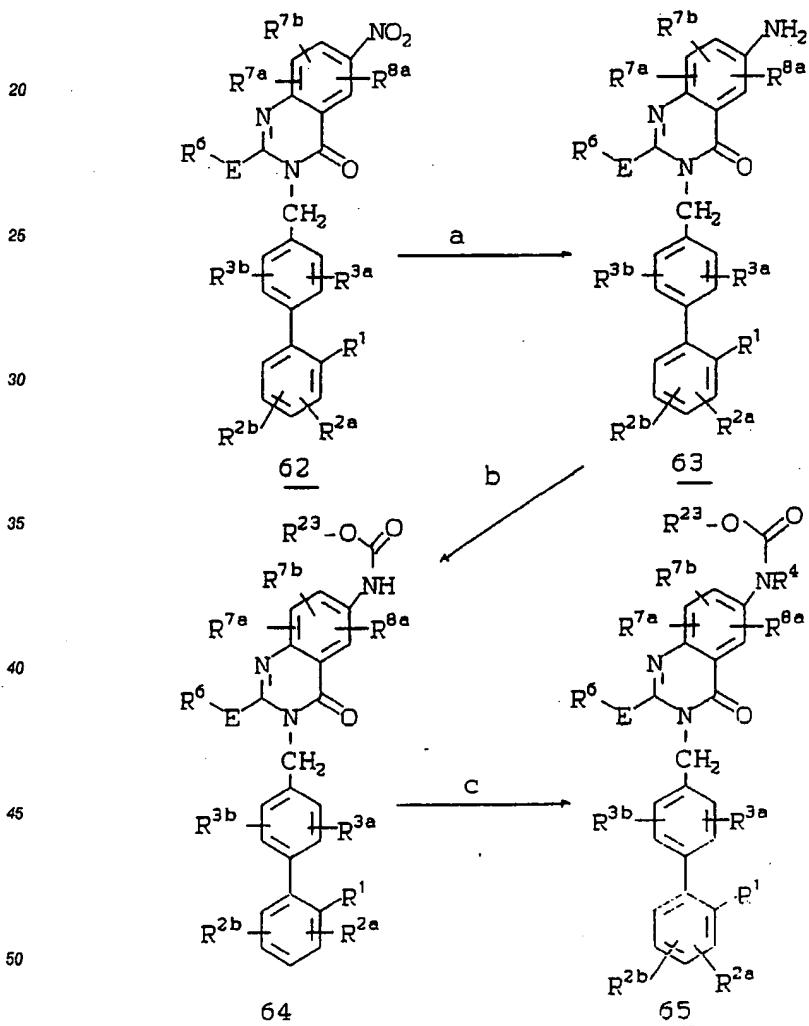
Further functionalization of compounds of Formula 1 where R^{8a} and R^{8b} is nitro is available through the following route (Scheme 22). The nitro group of 62 may be reduced to the amine 63 by reduction with hydrogen over palladium on carbon. The amine may then be acylated with acid chlorides to give amides under basic conditions. The acylation of the amine with chloroformates is best carried out in the presence of sodium hydride to form the anilinium anion. This anion reacts quickly with chloroformates to give the carbamates 64. The carbamate may be isolated and then deprotonated with lithium hexamethyldisilazide and alkylated to give the N,N-dialkylated carbamates 65. Alternatively this process may be carried out in

one pot by first preforming the anilinium anion, acylating it and then deprotonating *in situ* and alkylating with R⁴ iodide group to give 65. The amine reacts slowly with isocyanates to give ureas 66. Trisubstituted ureas 67 may be prepared from the benzyl carbamate 64 (R²³ = benzyl) by treatment with the magnesium salt of a secondary amine. The trisubstituted ureas may be N-alkylated by deprotonation with lithium hexamethyl-5 disilazide and alkylation with an R⁴ iodide to give 68. The amine may be further derivatized or converted to other groups by means of chemical procedures well known to those skilled in the art.

SCHEME 22

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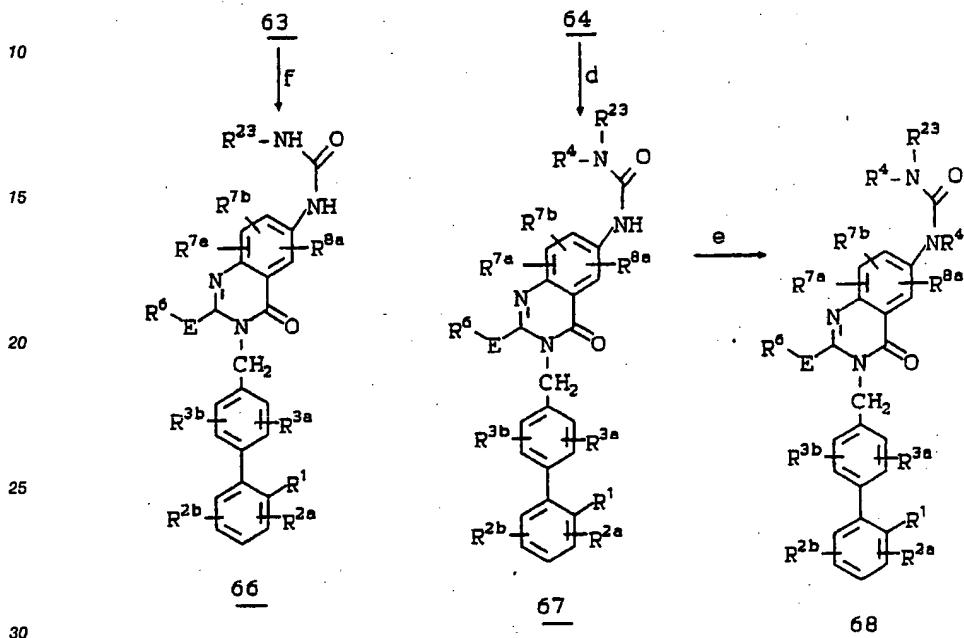
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SCHEME 22 (Cont'd)

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- a. H_2 , 10% Pd/C, Et Ac
- b. NaH , $ClCOR^{23}$, DMF
- c. $LiN(TMS)_2$, R^4I
- d. $MeMgBr$, R^4NHR^{23} , THF, reflux
- e. $LiN(TMS)_2$, R^4I , DMF
- f. $R^{23}NCO$, CH_2Cl_2

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 It will be appreciated by those skilled in the art that the protecting groups used in these syntheses will be chosen to be compatible with subsequent reaction conditions. Ultimately, they will be removed to generate the active compounds of formula (I). For example, R¹ as carboxyl is often protected as its t-butyl ester which in the last step is removed by treatment with trifluoroacetic acid. Aqueous acetic acid employed overnight is a preferred method to remove a trityl protecting group to liberate an R¹ tetrazole group.

The compounds of this invention form salts with various inorganic and organic acids and bases which are also within the scope of the invention. Such salts include ammonium salts, alkali metal salts like sodium and potassium salts, alkaline earth metal salts like the calcium and magnesium salts, salts with organic bases; e.g., dicyclohexylamine salts, N-methyl-D-glucamine, salts with amino acids like arginine, lysine, and the like. Also, salts with organic and inorganic acids may be prepared; e.g., HCl, HBr, H₂SO₄, H₃PO₄, methane-sulfonic, toluensulfonic, maleic, fumaric, camphorsulfonic. The non-toxic, physiologically, acceptable salts are preferred, although other salts are also useful; e.g., in isolating or purifying the product.

The salts can be formed by conventional means such as by reacting the free acid or free base forms of the product with one or more equivalents of the appropriate base or acid in a solvent or medium in which the salt is insoluble or in a solvent such as water which is then removed in vacuo or by freeze-drying or by exchanging the cations of an existing salt for another cation on a suitable ion exchange resin.

Angiotensin II (All) is a powerful arterial vasoconstrictor, and it exerts its action by interacting with specific receptors present on cell membranes. The compounds described in the present invention act as competitive antagonists of All at the receptors. In order to identify All antagonists and determine their 40 efficacy in vitro, the following two ligand-receptor binding assays were established.

Receptor binding assay using rabbit aortae membrane preparation:

45 Three frozen rabbit aortae (obtained from Pel-Freeze Biologicals) were suspended in 5mM Tris-0.25M Sucrose, pH 7.4 buffer (50 ml) homogenized, and then centrifuged. The mixture was filtered through a cheesecloth and the supernatant was centrifuged for 30 minutes at 20,000 rpm at 4°C. The pellet thus obtained was resuspended in 30 ml of 50mM Tris-5 mM MgCl₂ buffer containing 0.2% Bovine Serum Albumin and 0.2 mg/ml Bacitracin and the suspension was used for 100 assay tubes. Samples tested for 50 screening were done in duplicate. To the membrane preparation (0.25 ml) there was added ¹²⁵I-Sar¹Ile⁸-angiotensin II [obtained from New England Nuclear] (10 μ l; 20,000 cpm) with or without the test sample and the mixture was incubated at 37°C for 90 minutes. The mixture was then diluted with ice-cold 50mM Tris-0.9% NaCl, pH 7.4 (4ml) and filtered through a glass fiber filter (GF/B Whatman 2.4" diameter). The filter was soaked in scintillation cocktail (10 ml) and counted for radioactivity using Packard 2660 Tricarb liquid scintillation counter. The inhibitory concentration (IC₅₀) of potential All antagonist which gives 50displacement of the total specifically bound ¹²⁵I-Sar¹Ile⁸-angiotensin II was presented as a measure of the efficacy of such compounds as All antagonists.

Receptor assay using Bovine adrenal cortex preparation

Bovine adrenal cortex was selected as the source of All receptor. Weighed tissue (0.1 g is needed for 100 assay tubes) was suspended in Tris.HCl (50mM), pH 7.7 buffer and homogenized. The homogenate 6 was centrifuged at 20,000 rpm for 15 minutes. Supernatant was discarded and pellets resuspended in buffer [Na₂HPO₄ (10mM)-NaCl (120mM)-disodium EDTA (5mM) containing phenylmethane sulfonyl fluoride (PMSF)(0.1mM)]. (For screening of compounds, generally duplicates of tubes are used). To the membrane 10 preparation (0.5 ml) there was added ³H-angiotensin II (50mM) (10μl) with or without the test sample and the mixture was incubated at 37 °C for 1 hour. The mixture was then diluted with Tris buffer (4ml) and filtered through a glass fiber filter (GF/B Whatman 2.4" diameter). The filter was soaked in scintillation cocktail (10ml) and counted for radioactivity using Packard 2660 Tricarb liquid scintillation counter. The inhibitory concentration (IC₅₀) of potential All antagonist which gives 50% displacement of the total specifically bound ³H-angiotensin II was presented as a measure of the efficacy of such compounds as All antagonists.

15 The potential antihypertensive effects of the compounds described in the present invention may be evaluated using the methodology described below:

Male Charles River Sprague-Dawley rats (300-375 gm) were anesthetized with methohexitol (Brevital; 50 mg/kg i.p.) and the trachea was cannulated with PE 205 tubing. A stainless steel pithing rod (1.5 mm thick, 150 mm long) was inserted into the orbit of the right eye and down the spinal column. The rats were 20 immediately placed on a Harvard Rodent Ventilator (rate - 60 strokes per minute, volume -1.1 cc per 100 grams body weight). The right carotid artery was ligated, both left and right vagal nerves were cut, and the left carotid artery was cannulated with PE 50 tubing for drug administration, and body temperature was maintained at 37 °C (by a thermostatically controlled heating pad which received input from a rectal temperature probe. Atropine (1 mg/kg i.v.) was then administered, and 15 minutes later propranolol (1 25 mg/kg i.v.). Thirty minutes later angiotensin II or other agonists were administered intravenously at 30-minute intervals and the increase in the diastolic blood pressure was recorded before and after drug or vehicle administration.

Using the methodology described above, representative compounds of the invention were evaluated and were found to exhibit an activity of at least IC₅₀<50μM thereby demonstrating and confirming the utility 30 of the compounds of the invention as effective All antagonists.

Thus, the compounds of the invention are useful in treating hypertension. They are also of value in the management of acute and chronic congestive heart failure. These compounds may also be expected to be useful in the treatment of secondary hyperaldosteronism, primary and secondary pulmonary hyperaldosteronism, primary and secondary pulmonary hypertension, renal failure such as diabetic nephropathy, 35 glomerulonephritis, scleroderma, glomerular sclerosis, proteinuria of primary renal disease, end stage renal disease, renal transplant therapy, and the like, renal vascular hypertension, left ventricular dysfunction, diabetic retinopathy and in the management of vascular disorders such as migraine, Raynaud's disease, luminal hyperplasia, and to minimize the atherosclerotic process. The application of the compounds of this invention for these and similar disorders will be apparent to those skilled in the art.

40 The compounds of this invention are also useful to treat elevated intraocular pressure and to enhance retinal blood flow and can be administered to patients in need of such treatment with typical pharmaceutical formulations such as tablets, capsules, injectables and the like as well as topical ocular formulations in the form of solutions, ointments, inserts, gels, and the like. Pharmaceutical formulations prepared to treat intraocular pressure would typically contain about 0.1% to 15% by weight, preferably 0.5% to 2% by weight, of a compound of this invention.

45 In the management of hypertension and the clinical conditions noted above, the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for oral administration, suppositories for rectal administration, sterile solutions or suspensions for parenteral or intramuscular administration, and the like. The compounds of this invention can be administered to patients (animals and human) in need of such treatment in dosages that will provide optimal pharmaceutical efficacy. Although the dose will vary from patient to patient depending upon the nature and severity of disease, the patient's weight, special diets then being followed by a patient, concurrent medication, and other factors which those skilled in the art will recognize, the dosage range will generally be about 1 to 1000 mg. per patient per day which can be administered in single or multiple doses. Preferably, the dosage range will be about 2.5 to 55 250 mg. per patient per day; more preferably about 2.5 to 75 mg. per patient per day.

The compounds of this invention can also be administered in combination with other antihypertensives and/or diuretics and/or angiotensin converting enzyme inhibitors and/or calcium channel blockers. For example, the compounds of this invention can be given in combination with such compounds as amiloride,

atenolol, bendroflumethiazide, chlorothalidone, chlorothiazide, clonidine, cryptenamine acetates and cryptenamine tannates, deserpidine, diazoxide, guanethidine sulfate, hydralazine hydrochloride hydrochlorothiazide, metolazone, metoprolol tartate, methyclothiazide, methyldopa, methyldopate hydrochloride, minoxidil, pargyline hydrochloride, polythiazide, prazosin, propranolol, *rauwolfia serpentina*, rescinnamine, 5 reserpine, sodium nitroprusside, spironolactone, timolol maleate, trichlormethiazide, trimethophan camsylate, benzthiazide, quinethazone, ticryfan, triamterene, acetazolamide, aminophylline, cyclothiazide, ethacrynic acid, furosemide, merethoxylline procaine, sodium ethacrynat, captopril, delapril hydrochloride, enalapril, enalaprilat, fosinopril sodium, lisinopril, pentopril, quinapril hydrochloride, ramipril, teprotide, 10 zofenopril calcium, diflusinal, diltiazem, felodipine, nicardipine, nifedipine, niludipine, nimodipine, nisoldipine, nitrendipine, and the like, as well as admixtures and combinations thereof.

Typically, the individual daily dosages for these combinations can range from about one-fifth of the minimally recommended clinical dosages to the maximum recommended levels for the entities when they are given singly.

To illustrate these combinations, one of the angiotensin II antagonists of this invention effective clinically 15 in the 2.5-250 milligrams per day range can be effectively combined at levels at the 0.5-250 milligrams per day range with the following compounds at the indicated per day dose range: hydrochlorothiazide (15-200 mg) chlorothiazide (125-2000 mg), ethacrynic acid (15-200 mg), amiloride (5-20 mg) furosemide (5-80 mg), propranolol (20-480 mg), timolol maleate (5-60 mg), methyldopa (65-2000 mg), felodipine (5-60 mg), 20 nifedipine (5-60 mg), and nitrendipine (5-60 mg). In addition, triple drug combinations of hydrochlorothiazide (15-200 mg) plus amiloride (5-20 mg) plus angiotensin II antagonist of this invention (3-200 mg) or hydrochlorothiazide (15-200 mg) plus timolol maleate (5-60) plus an angiotensin II antagonist of this invention (0.5-250 mg) or hydrochlorothiazide (15-200 mg) and nifedipine (5-60 mg) plus an angiotensin II antagonist of this invention (0.5-250 mg) are effective combinations to control blood pressure in 25 hypertensive patients. Naturally, these dose ranges can be adjusted on a unit basis as necessary to permit divided daily dosage and, as noted above, the dose will vary depending on the nature and severity of the disease, weight of patient, special diets and other factors.

Typically, these combinations can be formulated into pharmaceutical compositions as discussed below.

About 1 to 100 mg. of compound or mixture of compounds of Formula I or a physiologically acceptable salt is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, 30 stabilizer, flavor, etc., in a unit dosage form as called for by accepted pharmaceutical practice. The amount of active substance in these compositions or preparations is such that a suitable dosage in the range indicated is obtained.

Illustrative of the adjuvants which can be incorporated in tablets, capsules and the like are the following: a binder such as gum tragacanth, acacia, corn starch or gelatin; an excipient such as microcrystalline 35 cellulose; a disintegrating agent such as corn starch, pregelatinized starch, alginic acid and the like; a lubricant such as magnesium stearate; a sweetening agent such as sucrose, lactose or saccharin; a flavoring agent such as peppermint, oil of wintergreen or cherry. When the dosage unitform is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as fatty oil. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For 40 instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain the active compound, sucrose as a sweetening agent, methyl and propyl parabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

Sterile compositions for injection can be formulated according to conventional pharmaceutical practice by dissolving or suspending the active substance in a vehicle such as water for injection, a naturally 45 occurring vegetable oil like sesame oil, coconut oil, peanut oil, cottonseed oil, etc., or a synthetic fatty vehicle like ethyl oleate or the like. Buffers, preservatives, antioxidants and the like can be incorporated as required.

The following examples illustrate the preparation of the compounds of formula (I) and their incorporation 50 into pharmaceutical compositions and as such are not to be considered as limiting the invention set forth in the claims appended hereto. All ¹H-NMR spectra were recorded on a Varian XL-300 Fourier transform spectrometer. Chemical shifts are reported as (parts per million) downfield from tetramethyl silane. Mass spectra were obtained from the Merck and Co. mass spectral facility in Rahway N.J. Analytical TLC was conducted on E.M. Merck precoated silica plates (0.25 mm in glass, Kieselgel 60 F₂₅₄) with UV visualization. All chromatography was conducted on E. M. Merck silica gel. All reactions were carried out 55 under an atmosphere of dry nitrogen under standard conditions for those skilled in the art.

PREPARATION OF BIPHENYL SYNTHETIC INTERMEDIATES:

2-t-Butoxycarbonyl-4'-methylbiphenyl

To a solution of p-bromotoluene (30g) in dry ether (150 ml) at -78°C, a solution of t-BuLi in pentane (1.7M) (210 ml) was added slowly over a period of 1.5 hours, using a dropping funnel. The bath was then 5 removed and the mixture was stirred at room temperature for an additional 2 hours. The content of the flask was then added slowly (using a cannula) at room temperature to a premixed solution of ZnCl₂ in ether (1M, 180 ml) and dry THF (360 ml). The mixture was stirred for 2 hours at that temperature and then the slurry was added (using a cannula) to a solution of 2-t-butoxycarbonyl iodobenzene (35.6 g) and NiCl₂(Ph₃P)₂ (2.1 g) in dry THF (360 ml). The mixture, after stirring at room temperature overnight (18 hours), was poured 10 slowly under stirring into ice-cold 0.5N HCl (1500 ml). The organic layer was separated, and the aqueous phase was extracted with ether (3 X 300 ml). The combined organic layer was washed with water, brine and then dried over MgSO₄. Removal of the solvent gave the crude product as an oil (32 g). The material was purified on a silica-gel flash column using ethyl acetate-hexane (1:12) to give the titled compound as an oil (24 g, 76%). ¹H NMR (CDCl₃): δ 1.24 (s, 9H), 2.42 (s, 3H), 7.2-7.8 (m, 8H); FAB-MS: m/e 269(M + H).

15

4Bromoethyl-2'-t-butoxycarbonylbiphenyl

To a solution of 2-t-butoxycarbonyl-4'-methylbiphenyl (25.3 g, 95 mmol) in CCl₄ (200 ml) were added 20 freshly opened N-bromosuccinimide (17.6 g, 0.099 mole) and dibenzoyl peroxide (2.28 g, 0.0094 moles). The mixture was refluxed for 4 hours, cooled to room temperature and filtered. The filtrate was washed with sat. NaHSO₃ (1x50 ml), sat. NaHCO₃ (1x50 ml), water (1x50 ml), sat. NaCl (1x50 ml) and dried over MgSO₄. The solution was filtered, and concentrated in vacuo. The residue was dissolved in 100 ml of hot hexane. Crystallization gradually took place as the solution cooled. The flask was finally cooled to -20°C 25 and the precipitate recovered by filtration. The solid was washed with ice cold hexanes and dried in vacuo to give 27 g (88%) of a white solid. ¹H-NMR (CDCl₃): 1.23 (s, 2H), 4.53 (s, 2H), 7.2-7.5 (m, 7H), 7.68 (d, 1H).

30 2-Cyano-4'-methylbiphenyl

To a solution of p-bromotoluene (30 g) in dry ether (150 ml) at -78°C, a solution of t-BuLi in pentane (1.7M) (210 ml) was added slowly over a period of 1.5 hours, using a dropping funnel. The bath was then removed and the mixture was stirred at room temperature for an additional 2 hours. The contents of the 35 flask was then added slowly (using a cannula) at room temperature to a premised solution of ZnCl₂ in ether (1M) (180 ml) and dry THF (360 ml). The mixture was stirred for 2 hours at that temperature and then the slurry was added (using a cannula) to a solution of 2-bromobenzonitrile (21.3 g) and NiCl₂(Ph₃P)₂ (2.1 g) in dry THF (300ml). The mixture, after stirring at room temperature overnight (18 hours), was poured slowly 40 under stirring into ice-cold 1N HCl (1500 ml). The organic layer was separated, and the aqueous phase was extracted with ether (3 X 300 ml). The combined organic layer was washed with water, brine and then dried over MgSO₄. Removal of the solvent gave the crude product as a semisolid mass (34 g). The material was purified on a silica-gel flash column using ethyl acetate-hexane (1:12) to give the desired nitrile as a low-melting solid (28 g, 88%). ¹H NMR (CDCl₃): 2.42 (s, 3H), 7.2-7.8 (m, 8H); FAB-MS: m/e 194 (M⁺ + 1).

45

Trimethylstannyl azide

To a concentrated solution of NaN₃ (1.2 kg, 18.5 moles) in water (3 L), a solution of trimethyltin chloride (600 g, 3 moles) in dioxane (400 ml) was added in three portions under vigorous stirring. A precipitate 50 formed instantaneously. The mixture, after stirring overnight at room temperature, was filtered. The residue was washed with water, and dried under suction and then in vacuo over P₂O₅. Yield 541 g (88%), mp 120-122°C.

55 5-[2-(4'-Methylbiphenyl)]tetrazole

To a solution of 2-cyano-4'-methylbiphenyl (390 g, 2.02 moles) in toluene (2.3 L) was added trimethyltin azide (525 g, 2.55 moles) at room temperature. The mixture was refluxed for 24 hours, cooled to room

temperature, filtered, washed with toluene and sucked dry in a funnel. The precipitate was resuspended in toluene (3.5 L) and THF (250 mL) was added. Anhydrous HCl was bubbled in at a moderate rate at room temperature to give a clear solution (45 minutes). Addition of HCl gas was continued for another 20 minutes with stirring whereupon a white precipitate formed. The reaction mixture was stirred overnight. The solid 5 product was filtered, washed with toluene followed with ether and then dried under vacuum. This produced 250 g (53% yield of the tetrazole. m.p. 152-154 °C; ¹H-NMR (CDCl₃): 2.40 (s, 3H), 7.19 (dd, 1H), 7.55 (m, 2H), 8.25 (dd, 1H).

10 N-Triphenylmethyl-5-[2-(4'-methylbiphenyl)]tetrazole

To a cloudy solution of 5-[2-(4'-methylbiphenyl)]tetrazole (250 g (1.06 mole) in CH₂Cl₂ (4 L) was added triphenylmethylchloride (310 g 1.11 mole) at room temperature. The reaction mixture was stirred and triethylamine (190 mL, 138 g, 1.36 mole) was added portionwise. After addition, the mixture was stirred at 15 reflux for 90 minutes. The solution was cooled to room temperature, washed with water (2x1 L) and dried over MgSO₄, filtered through a silica gel plug and concentrated on the rotovap to a solid. This was crystallized from toluene to give the product as an off-white solid (425 g, 84%); m.p. 166-168 °C; ¹H-NMR (CDCl₃): 2.28 (s, 3H), 6.9-7.05 (m, 10H), 7.2-7.5 (m, 12H), 7.9 (dd, 1H).

20 N-Triphenylmethyl-5-[2-(4'-bromomethylbiphenyl)]tetrazole

To a solution of N-triphenylmethyl-5-[2-(4'-methylbiphenyl)]tetrazole (425 g, 0.89 moles) in CCl₄ (4.0 L) were added N-bromosuccinimide (159 g, 0.89 mole) and dibenzoyl peroxide (22 g, 0.089 moles). The 25 mixture was refluxed for 2 hours, cooled to room temperature and filtered. The filtrate was concentrated in vacuo to give a thick oil. The addition of ether (2.0 L) to this oil resulted in a clear solution followed by crystallization, filtration gave a white solid (367 g, 74%). m.p. 137-139.5 °C; ¹H-NMR (CDCl₃): 4.38 (s, 2H), 6.9-8.0 (m, 23H).

30 N-Triphenylmethyl-5-[2-(4'-aminomethylbiphenyl)]tetrazole

To a suspension of 11.15 g (22 mmol) of N-triphenylmethyl-5-[2-(4'-bromomethylbiphenyl)]tetrazole in 55 mL of dry DMSO was added 1.23 g (25 mmol) of LiN₃. The mixture gradually cleared and was replaced 35 by a new white precipitate. The mixture was stirred for 6 hours and filtered. The precipitate was washed with 50 mL of water. Some additional precipitate formed in the mixed filtrate; this was refiltered and the residue washed with 30 mL of MeOH and 100 mL of water. The solid product was dried in vacuo overnight. The crude azide (9.89 g, 20.8 mmol) was dissolved in 50 mL of dry THF and treated with 5.73 g (22 mmol) of triphenylphosphine portionwise. N₂ evolution was observed during the addition. After 4 hours the solution 40 was treated with 0.63 mL (34 mmol) of water and stirred over night. The solution was concentrated in vacuo and the residue purified by flash chromatography over silica gel eluting with 95:5:0.01 CHCl₃:MeOH:NH₄OH. 6.83 g (15.4 mmol) of a white solid was recovered. 69% overall yield. ¹H-NMR (CDCl₃): 3.74 (s, 2H), 6.88 (m, 5H), 7.06 (q, 4H, J=8.1Hz), 7.22-7.52 (m, 13H), 7.95 (m, 1H).

45 Preparation of Additional Functionalized Biphenyls

50 Preparation of: N-Triphenyl-5-(4'-bromomethyl-4-chlorobiphen-2-yl)tetrazole

Step 1: 2-Cyano-4'-methyl-4-nitrobiphenyl

To a solution of p-tolyltrimethyltin (389 mg, 1.525 mmol) in dry toluene (5 mL) under N₂ was added 2-55 bromo-5-nitro-benzonitrile (276 mg, 1.22 mmol) and Pd(PPh₃)₄ (176 mg; 10 mol %). The reaction was stirred at reflux under N₂ for 24 hours and then cooled to room temperature. The mixture was diluted with EtOAc and the solid was removed by filtration through a pad of celite. The filtrate was concentrated in vacuo and the residue was purified by flash chromatography on a silica column eluting with Hex/EtOAc

(10:1) to afford 214 mg (74%) of the titled compound as a slightly yellow solid. ^1H NMR (300 MHz, CDCl_3) δ 2.42 (s, 3H), 7.32 (d, 2H), 7.48 (d, 2H), 7.69 (d, 1H), 8.45 (dd, 1H), 8.61 (s, 1H).

5 Step 2: N' -Triphenylmethyl-5-(4'-methyl-4-nitrobiphen-2-yl)tetrazole

The titled compound was prepared starting from 2-cyano-4-nitro-4'-methylbiphenyl (step 1) according to procedures described in European Patent Application EP 0,291,969. ^1H NMR (300 MHz, CDCl_3) δ 2.28 (s, 3H), 6.89 (d, 6H), 6.98 (ABq, 4H), 7.22-7.37 (comp, 9H), 7.56 (d, 1H), 8.31 (dd, 1H), 8.75 (d, 1H).

10

Step 3: N -Triphenylmethyl-5-(4-chloro-4'-methylbiphen-2-yl)tetrazole

A solution of N -Triphenylmethyl-5-(4'-methyl-4-nitrobiphen-2-yl)tetrazole (0.115 g, 0.224 mmol) in 15 MeOH/DMF (2 mL/12 mL) was submitted to hydrogenation at 40 psi H_2 with 10% Pd on carbon (50 mg) at room temperature for 1 hour. The reaction was filtered through celite and the filtrate was concentrated in *vacuo*. The triphenyl methyl group had been lost during the hydrogenation. The crude 4-amino compound was dissolved in glacial acetic acid (3 mL) and added slowly to a cooled (0 °C) solution of NaNO_2 (28.8 mg, 0.417 mmol) in conc. sulfuric acid (1 mL). The diazonium solution was stirred well for 2 hours then slowly 20 added to a cooled (0 °C) solution of CuCl (0.449 g, 20 equiv) in conc. HCl. This mixture was stirred for 30 minutes and then poured over H_2O and extracted with $\text{Et}_2\text{O}/\text{EtOAc}$. The combined organic extracts were washed with H_2O and brine, dried over MgSO_4 and concentrated in *vacuo*. The product was purified by flash chromatography on a silica column eluting with Hex/EtOAc/HOAc (80:20; 1) to afford 27 mg (45% for 25 2 steps) of 5-(4-chloro-4'-methyl-biphen-2-yl)tetrazole. The free tetrazole was dissolved in CH_2Cl_2 (3.5 mL) and NEt_3 (0.035 mL, 2.5 equiv) and Ph_3CCl (27 mg, 1.0 equiv) were added. After 30 minutes the reaction was diluted with Et_2O washed with 10% citric acid, 1N NaOH and brine. The organic was dried over anhydrous MgSO_4 and concentrated in *vacuo* to afford 51.2 mg (100%) of crude N -triphenylmethyl-5-(4-chloro-4'-methyl-biphen-2-yl)tetrazole. ^1H NMR (300 MHz, CDCl_3) δ 2.26 (s, 3H), 6.91 (d, 6H), 6.94 (ABq, 4H), 7.20-7.25 (comp, 7H), 7.43 (dd, 1H), 7.99 (dd, 1H).

30

Step 4: N -Triphenylmethyl-5-(4'-bromomethyl-4-chlorobiphen-2-yl)tetrazole

The titled compound was prepared starting from N -Triphenylmethyl-5-(4-chloro-4'-methyl-biphen-2-yl)tetrazole (step 1 to 3) according to procedures described in European Patent Application EP 0,291,969.

Preparation of: 4-Bromomethyl-2'-nitrobiphenyl

40

Step 1: 4-Methyl-2'-nitrobiphenyl

A 1 L three-necked 24/40 round-bottom flask equipped with a mechanical stirrer, a 250 mL constant pressure addition funnel with a nitrogen inlet at the top, and a septum was flame dried, cooled and then 45 charged with a solution of 29.07 g (0.17 mol) of p-bromotoluene in 100 mL of anhydrous tetrahydrofuran under a nitrogen atmosphere. The solution was stirred and cooled to -78 °C and 200 mL (0.34 mol) of a 1.7 M solution of t-butyllithium in pentane was added via the addition funnel over 30 minutes. When the addition was complete, the cooling bath was removed and the reaction mixture was stirred for 30 minutes and allowed to warm to room temperature. The dropping funnel was next charged with 170 mL (0.17 mol) of 50 a 1.0 M solution of zinc chloride in diethylether which was added to the reaction mixture over a 10 minute period. A separate 1 L three-necked 24/40 round-bottom flask equipped with a mechanical stirrer, a nitrogen inlet and a septum, was flame dried, cooled and then charged with 4.04 g (6.0 mmol) of bis-(triphenylphosphine)palladium(II) chloride and 50 mL of anhydrous tetrahydrofuran under a nitrogen atmosphere. The stirrer was started and 8.0 mL of a 1.5 M solution (12 mmol) of diisobutylaluminum hydride 55 in toluene was added to the suspension via syringe. The catalyst was stirred an additional 10 minutes at room temperature, and then a solution of 23.23 g (0.115 mol) of 1-bromo-2-nitrobenzene in 100 5mL of anhydrous tetrahydrofuran was added. The suspension of the tolylzinc chloride was then transferred to the second flask via a wide diameter cannula. The reaction mixture was stirred an additional 45 minutes at room

temperature, then most of the tetrahydrofuran was removed on a rotary evaporator. The resulting oil was partitioned between ethyl acetate and 1.0 N hydrochloric acid. The organic layer was washed successively with water and brine, then dried (MgSO_4), filtered and evaporated. The residual oil was purified on a silica gel flash chromatography column eluted with 10% ethyl acetate-hexane to afford after-evaporation and 5 drying in *vacuo* 15.43 g (63%) of the product as a viscous yellow oil: NMR (CDCl_3): δ 2.36 (s, 3H), 7.16-7.24 (m, 4H), 7.38-7.46 (m, 2H), 7.55-7.62 (m, 1H), 7.80 (d, J =10 Hz, 1H); MS (FAB) m/e 214 (MH^+).

Step 2: 4-Bromomethyl-2'-nitrobiphenyl

10 A 2 L 24/40 three necked round-bottom flask equipped with a mechanical stirrer, a reflux condenser and a stopper, was charged with 15.427 g (72 mmol) of 4-methyl-2'-nitro[1,1'-biphenyl], 1.2 L of carbon tetrachloride, 14.164 g (80 mmol) of N-bromosuccinimide, and 0.50 g of 2,2'-azobis-(2-methylpropionitrile). The stirred reaction mixture was refluxed under a nitrogen atmosphere for 4 hours, then cooled to room 15 temperature and filtered. The filtrate was evaporated *in vacuo* and the residual oil was purified on a silica gel flash chromatography column eluted with 10% ethyl acetate-hexane. Evaporation of the pure fractions afforded the product as a yellow crystalline solid (7.83 g, 37%) which had: mp 109-110 °C; NMR (CDCl_3): δ 4.52 (s, 2H), 7.24-7.30 (m, 2H), 7.40-7.52 (m, 4H), 7.58-7.65 (m, 1H), 7.86 (d, J =10 Hz, 1H); MS (FAB) m/e 294 (MH^+).

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Preparation of N-Triphenylmethyl-5-(4-fluoro-4'-bromomethyl-biphen-2-yl)tetrazole

25 Step 1: 2-cyano-4-fluoro-4'-methylbiphenyl

A solution of p-tolyltrimethyltin (1.26 g; 4.96 mmol) in dry toluene (8 mL) was degassed with a stream of N_2 for ca. 5 min. To this solution under N_2 was added 2-bromo-5-fluoro-benzonitrile (0.901 g; 4.51 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (260 mg; 5 mol %). The reaction was stirred at reflux under N_2 for 12 hr and then cooled to room temperature. The reaction mixture was filtered through a pad of celite and the filtrate was concentrated *in vacuo*. The product was purified by flash chromatography on a silica column eluting with $\text{Hex}/\text{CH}_2\text{Cl}_2$ to afford 0.606 g (64%) of the titled compound as a slightly yellow solid. ^1H NMR (300 MHz, CDCl_3) δ 2.40 (s, 3H), 7.28 (d, 2H), 7.34 (dd, 1H), 7.40 (d, 2H), 7.44 (t, 1H), 7.46 (dd, 1H); FAB mass spectrum, m/e 211 (m+, calcd for $\text{C}_{14}\text{H}_{10}\text{NF}$, 211).

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Step 2: N-Triphenylmethyl-5-(4-fluoro-4'-methylbiphen-2-yl)tetrazole

The titled compound was prepared starting from 2-cyano-4-fluoro-4'-methylbiphenyl (step 1) according 40 to procedures described in European Patent Application EP 0,291,969.

Step 3: N-Triphenylmethyl-5-(4-fluoro-4'-bromomethyl-biphen-2-yl)tetrazole

45 To a solution of N-Triphenylmethyl-5-(4-fluoro-4'-methyl-biphen-2-yl)tetrazole (454.4 mg; 0.9161 mmol) in dry CCl_4 (8 mL) was added N-bromosuccinimide (179.2 mg; 1.1 eq) and a catalytic amount of AIBN. The reaction was heated to reflux (105-115 °C) under N_2 . After 3 hrs. the reaction was cooled and filtered through a cotton plugged pipet to remove the succinimide formed. The solvent was removed and replaced by $\text{EtOAc}/\text{Et}_2\text{O}$. The reaction was washed with 1 N NaOH and brine. The organic solution was dried over 50 anhydrous MgSO_4 , filtered, and concentrated *in vacuo* to afford the product. The crude product was used in the next reaction.

PREPARATION OF 2-ALKYL-QUINAZOLIN-4(1H)-ONES

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EXAMPLE 1

2-Butyl-6-methylquinazolin-4(1H)-one

To a solution of 3.0 g (20 mmol) of 2-amino-5-methylbenzoic acid in 20 mL of dry DMF at 0°C was 5 added 200 mg of DMAP followed by 6.07 g (60 mmol) of triethyl amine and 5.02 g (40 mmol) of valeryl chloride. The resulting mixture was stirred at 0°C for 30 minutes. The mixture was heated to 110°C and monitored by TLC for the formation of the intermediate quinoxazolone (r_f =0.8, 40%EtAc/hexane). Following complete formation of the intermediate 10 g (100 mmol) of NH_4CO_3 was added cautiously. Heating was 10 continued to ensure consumption of the quinoxazolone and formation of the polar (r_f =0.4, 40%EtAc/hexane) quinazolin-4(1H)-one. The reaction mixture was concentrated in vacuo and the residue was taken up in 50 mL of ether and 50 mL of water. The mixture was filtered and the filtrate discarded after 15 washing the residue with 20 mL of ether. The residue was recrystallized from MeOH to give 1.07 g (5 mmol) of a white crystalline solid. 25% yield overall. $^1\text{H-NMR}$ (CDCl_3): 0.94 (t, 3H, $J=6.7\text{Hz}$), 1.50 (m, 2H), 1.83 (m, 2H), 2.49 (s, 3H), 2.78 (t, 2H), 7.60 (m, 2H), 8.05 (m, 1H). Anal ($\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}$), C, H, N.

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EXAMPLE 2

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6-Methyl-2-propylquinazoline-4(1H)-one

The 2-propyl derivative was prepared in the identical fashion as the 2-butyl derivative through the use of 25 butyryl chloride in place of valeryl chloride. The product was recrystallized from hexane/acetone to give white crystals. 32% yield. $^1\text{H-NMR}$ (CDCl_3): 11.51 (bs, 1H), 8.08 (s, 1H), 7.60 (s, 2H), 2.78 (3 line m, 2H), 2.01 (s, 3H), 1.92 (m, 2H), 1.09 (t, 3H).

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EXAMPLE 3

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2-Butyl-7-methylquinazoline-4(1H)-one

Same procedure as in Example 1 with valeroyl chloride and 2-amino-4-methylbenzoic acid. The product was recrystallized from MeOH recovering 0.91 g (4.2 mmol). 21% yield overall. $^1\text{H-NMR}$ (CDCl_3): 0.99 (t, 3H, $J=7.4\text{ Hz}$), 1.49 (m, 2H), 1.86 (m, 2H), 2.50 (s, 3H), 2.76 (t, 2H, $J=7.81\text{ Hz}$), 7.28 (d, 1H, $J=8.3\text{ Hz}$), 40 7.49 (s, 1H), 8.15 (d, 1H, $J=8.3\text{Hz}$). Anal ($\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}$), C, H, N.

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EXAMPLE 42-Butyl-naphtho[2,3-e]quinazoline-4(1H)-one

50 Same procedure as in Example 1 with valeroyl chloride and 2-aminonaphthoic acid. Product was recrystallized from MeOH. A contaminant co-crystallizes with the desired product. The contaminant is 25% of the product by $^1\text{H-NMR}$. Recovered 1.6 g (59% yield). $^1\text{H-NMR}$ (CDCl_3): 0.97 (t, 3H, $J=7.3\text{ Hz}$), 1.42 (m, 2H), 1.75 (m, 2H), 2.48 (t, 2H, $J=7.4\text{ Hz}$), 7.42 (t, 1H, $J=7.8\text{ Hz}$), 7.54 (t, 1H, $J=8.3\text{ Hz}$), 7.77 (d, 1H, $J=7.8\text{ Hz}$), 7.82 (d, 1H, $J=8.31\text{ Hz}$), 8.07 (s, 1H), 9.08 (s, 1H), 10.89 (bs, 1H).

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EXAMPLE 5

2-Butyl-5-methylquinazoline-4(1H)-one

Same procedure as in Example 1 with valeroyl chloride and 2-amino-6-methylbenzoic acid on a 16 mmol scale. The concentrated reaction mixture was diluted with 50 mL ether and 50 mL H₂O. The mixture was agitated for several minutes and then filtered *in vacuo*. On filtration further crystalline material formed in the filtrate. The filtrate was filtered again. This procedure was repeated a further two times. The precipitates were collected and combined. The ethereal phase was decanted from the aqueous phase, and concentrated to 15 mL. 25 mL of hexanes was then added and the mixture filtered. The combined precipitates were recrystallized from MeOH/H₂O to give 0.73 g (3.37 mmol) of fluffy white crystals. 21% yield. ¹H-NMR (CDCl₃): 0.98 (t, 3H, J = 7.38 Hz), 1.48 (m, 2H), 1.87 (m, 2H), 2.75 (dd, 2H, J = 8.09 Hz), 2.89 (s, 3H), 7.20 (d, 1H, J = 6.73 Hz), 7.56 (m, 2H), 11.68 (bs, 1H).

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EXAMPLE 62-Butyl-6,8-dimethylquinazoline-4(1H)-one

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Same procedure as in Example 1 with valeroyl chloride and 2-amino-5,8-dimethylbenzoic acid on a 12 mmol scale. The product collected from filtration of the ether/water mixture was recrystallized from MeOH. ¹H-NMR and TLC indicated that the product isolated was a 50% mixture of the desired quinazoline and a contaminant. An aliquot of 0.5 g of this material was concentrated onto 5 mL of flash silica and applied to the surface of a flash chromatography column. The column was eluted with 60% EtAc/hexanes. The first eluted compound (0.14 g) was collected as a TLC homogeneous sample of the desired product. ¹H-NMR (CDCl₃): 0.99 (t, 3H, J = 7.32 Hz), 1.48 (m, 2H), 1.85 (m, 2H), 2.44 (s, 3H), 2.58 (s, 3H), 2.75 (dd, 2H, J = 7.87, 7.87 Hz), 7.43 (s, 1H), 7.91 (s, 1H), 10.70 (bs, 1H).

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EXAMPLE 7

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2-Butyl-8-methylquinazoline-4(1H)-one

Same procedure as in Example 1 with valeroyl chloride and 2-amino-6-methylbenzoic acid on a 1 mmol scale. The concentrated reaction mixture was diluted with 20 mL ether/20 mL H₂O. The mixture was filtered. The ethereal phase was separated, dried (MgSO₄), filtered and concentrated. The residue was flash chromatographed over silica eluting with 50% EtAc/hexanes to give rise to 48 mg (0.22 mmol) of a fluffy yellow solid. 22% yield. ¹H-NMR (CDCl₃): 1.02 (t, 3H), 1.52 (m, 2H), 1.88 (m, 2H), 2.62 (s, 3H), 2.79 (dd, 2H), 7.35 (dd, 1H), 7.61 (d, 1H), 8.12 (d, 1H). FABMS: 217 (M⁺ + 1) calc for C₁₃H₁₆N₂O.

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EXAMPLE 8

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2-Butyl-6-isopropylquinazolin-4(1H)-one

Same procedure as in Example 1 with valeroyl chloride and 2-amino-5-isopropylbenzoic acid on a 16 mmol scale. The concentrated reaction mixture was partitioned between 20 mL water and 20 mL of ether. A fine white precipitate was removed by filtration and recrystallized from MeOH/water. The first crop gave rise to 0.56 g of fluffy white crystals. ¹H-NMR (CDCl₃): 0.99 (t, 3H, J = 7.3Hz), 1.32 (d, 6H, J = 6.89Hz), 1.48 (m, 2H), 1.85 (m, 2H), 2.77 (3 line m, 2H, J = 7.9Hz), 3.06 (m, 1H), 7.65 (m, 2H), 8.11 (s, 1H), 11.22 (bs, 1H).

FABMS: 245 ($M^+ + 1$) calc for $C_{15}H_{20}N_2O$.

EXAMPLE 9

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2-Butyl-6-thiomethylquinazolin-4(1H)-one

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Same procedure as that described in Example 1. However on addition of ether/water to the reaction mixture a precipitate of the quinazolinone was not formed. The aqueous phase was extracted with ether and the combined ethereal extracts were washed with brine and dried over $MgSO_4$. The mixture was filtered and concentrated *in vacuo* to give a mixture of the desired product and 2-(N-valeroyl-amino)-5-thiomethylbenzamide. This mixture was heated with 2 equivalents of 1N NaOH solution in water at $100^\circ C$ until a clear solution was obtained. The solution was cooled, acidified, and filtered to give a pale yellow precipitate. The product was recrystallized from MeOH to give a 73% overall yield of the title compound. 1H -NMR ($CDCl_3$ -300MHz): 1.00 (t, 3H, $J = 7.3$ Hz), 1.50 (m, 2H), 1.86 (m, 2H), 2.58 (s, 3H), 2.76 (3 line m, 2H, $J = 7.9$ Hz), 7.62 (m, 2H), 8.03 (d, 1H, $J = 1.9$ Hz), 11.11 (bs, 1H).

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EXAMPLE 10

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2-Butyl-6-nitroquinazolin-4(1H)-one

To a mixture of 326 mg (2 mmol) of 2-cyano-4-nitroaniline in 10 mL of CH_2Cl_2 at $0^\circ C$ was added 0.34 mL (2.4 mmol) of triethylamine and 25 mg of DMAP. To this mixture was added 0.26 mL of valeryl chloride dropwise. The reaction mixture was allowed to warm to room temperature over 1.5 hours and then concentrated *in vacuo*. The residue was dissolved in 40 mL of EtAc and washed with 25 mL of water, 25 mL of saturated $NaHCO_3$ and 25 mL of brine. The organic phase was dried over Na_2SO_4 , filtered and concentrated. The residue (0.46 g) was purified by flash chromatography. The residue was absorbed onto 0.6 g of silica which was applied to the surface of a 5.5" x 75" silica flash chromatography column. The product was eluted with 20% EtAc/hexanes to give 0.21 g of N-valeryl-2-cyano-4-nitro-anilide (44% yield). 0.1 g (0.42 mmol) of the amide was dissolved in 1.5 mL of MeOH. To this solution was added 138 μ L of a 30% hydrogen peroxide solution followed by 330 μ L of a 3N NaOH solution. The solution was refluxed for 1.5 hours, cooled and concentrated *in vacuo*. The residue was dissolved in 10 mL of water. Dropwise addition of a saturated solution of NH_4Cl caused the product to precipitate out as 90 mg (0.36 mmol) of a yellow powder. (87 % yield). 1H -NMR ($CDCl_3$): 1.02 (t, 3H, $J = 7.32$ Hz), 1.52 (m, 2H), 1.90 (m, 2H), 2.82 (dd, 2H, $J = 8.03$ Hz), 7.82 (d, 1H, $J = 9.01$ Hz), 8.56 (dd, 1H, $J = 2.6, 8.8$ Hz), 9.14 (d, 1H, $J = 2.71$ Hz).

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EXAMPLE 11

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2-Butylquinazolin-4(1H)-one

To a solution of 500 mg 2-aminobenzonitrile (4.23 mmol), 514 mg triethylamine (5.08 mmol), and 50 mg DMAP (0.41 mmol) in 6 mL CH_2Cl_2 at $0^\circ C$ was added 562 mg valeryl chloride (4.66 mmol) dropwise over 1 minute. The mixture was warmed to room temperature and stirred for twenty minutes. The mixture was then diluted with water and brine and then was extracted three times with ether. The combined organic material was dried over $MgSO_4$, stripped of solvent *in vacuo*, and was purified by flash chromatography eluting with 20% ethyl acetate in hexane to give 2-valerylamido-benzonitrile. R_f 0.22 in 20% ethyl acetate in hexane. 1H NMR (300 MHz, $CDCl_3$): 8.42 (d, 1H), 7.60-7.10 (m, 2H), 6.72 (m, 1H), 4.40 (br s, 1H), 2.46 (t,

2H), 1.74 (m, 2H), 1.43 (m, 2H), 0.97 (t, 3H).

To a solution of 5.1 g of the amide in 90 mL methanol were added 21 mL 3N NaOH and 10 mL 30% H₂O₂ at room temperature. The mixture was refluxed for 30 minutes and concentrated *in vacuo*. Water and sat. NH₄Cl was added and the mixture extracted 3 times with ether. The combined organic extracts were 5 dried over MgSO₄, filtered and concentrated *in vacuo* and the residue was recrystallized from hexane/acetone to give two crops of the product as white needles. 2.2 g, 43% yield. R_f: 0.16 in 20% EtAc in CH₂Cl₂. ¹H-NMR (CDCl₃): 8.29 (m, 1H), 7.81-7.68 (m, 2H), 7.47 (m, 1H), 2.79 (3 line m, 2H), 1.87 (m, 2H), 1.51 (m, 2H), 1.00 (t, 1H).

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EXAMPLE 12

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6-Bromomethyl-2-butylquinazolin-4(1H)-one

To a suspension of 2.6 g (12 mmol) of the product of Example 2 in 100 mL of dry CCl₄ was added 2.56 g of N-bromosuccinimide followed by 200 mg of benzoyl peroxide. The reaction mixture was heated to 20 reflux for 45 minutes at which time a precipitate formed throughout. The reaction mixture was concentrated *in vacuo* and the residue partitioned between 150 mL of EtAc and 100 mL of water. The mixture was shaken and then filtered to give 1.59 g of the title compound (45% yield). The filtrate was separated into two phases and the organic phases was washed with 75 mL of sat. NaHCO₃ solution followed by 75 mL of water and 75 mL of brine. The organic phase was dried over MgSO₄, filtered and the filtrate was 25 concentrated *in vacuo*. The residue was purified by recrystallization from EtAc to give 0.52 g (1.76 mmol) of the same product as was recovered above. Total yield 60%. ¹H-NMR CDCl₃: 1.00 (t, 3H, J = 7.33 Hz), 1.49 (m, 2H), 1.84 (m, 2H), 2.77 (3 line m, 2H, J = 7.7 Hz), 4.61 (s, 2H), 7.68 (d, 1H, J = 8.4 Hz), 7.80 (dd, 1H, J = 8.4, 2.1 Hz), 8.27 (d, 1H, J = 2.1 Hz), 11.02 (bs, 1H).

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EXAMPLE 13

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5-Bromomethyl-2-butylquinazolin-4(1H)-one

The product of Example 5 was treated as in Example 13 to give a 71% yield of a white solid. ¹H-NMR CDCl₃: 1.0 (t, 3H, J = 7.3 Hz), 1.53 (m, 2H), 2.90 (m, 2H), 2.81 (3 line m, 2H, J = 7.98 Hz), 5.31 (s, 2H), 40 7.45 (m, 1H), 7.71 (m, 2H), 11.28 (bs, 1H).

EXAMPLE 14

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6-Acetoxyethyl-2-butylquinazolin-4(1H)-one

To a solution of 2.1 g (7.0 mmol) of the quinazolinone prepared in Example 12 in 15 mL of dry DMF 50 was added 1.74 g (20.0 mmol) of sodium acetate. The mixture was heated to 60 °C for 3 hours. The reaction mixture was concentrated *in vacuo* and the residue dissolved in 100 mL of CH₂Cl₂. The solution was washed with water (3x20 mL), brine (1x20 mL) and dried over MgSO₄. The mixture was filtered and concentrated *in vacuo*. The residue was recrystallized from MeOH/H₂O to give 1.31 g (4.8 mmol) of a 55 colorless solid. 68% yield. ¹H-NMR (CDCl₃): 0.99 (t, 3H, J = 7.32 Hz), 1.50 (m, 2H), 1.83 (m, 2H), 2.14 (t, 3H), 2.77 (3 line m, 2H, J = 7.71 Hz), 5.23 (s, 2H), 7.69-7.78 (m, 2H), 8.25 (s, 1H), 10.90 (bs 2H).

EXAMPLE 15

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5-Acetoxymethyl-2-butylquinazolin-4(1H)-one

The product of Example 13 was treated as in Example 15 to give after recrystallization from EtAc a 77% yield of the desired acetylated product. ¹H-NMR (CDCl₃): 0.98 (t, 3H, J=7.38Hz), 1.50 (m, 2H), 1.88 (m, 2H), 2.19 (s, 3H), 2.77 (3 line m, 2H, J=7.93 Hz), 5.85 (s, 2H), 7.48 (m, 1H), 7.70 (m, 2H), 11.65 (bs, 1H).

EXAMPLE 16

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6-Nitro-2-propylquinazolin-4(1H)-one.

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To a solution of 16.3 g (0.1 mol) of 2-amino-5-nitrobenzonitrile in 200 ml of CH₂Cl₂ at 0°C was added 21 ml (0.15 mol) of triethyl amine followed by 0.3 g of DMAP and 11.71 g (0.11 mol) of butyryl chloride. The reaction mixture was warmed to room temperature and then heated over night at 50°C. The solution was washed with 1N HCl (1x20 ml), water (1x20 ml), saturated NaHCO₃ (2x20 ml) and brine (1x20 ml) and dried over MgSO₄. The solution was filtered and concentrated in vacuo. The residue was dissolved in 200 ml of MeOH to which was added 44 ml (0.22 mol) of 5M NaOH solution followed by the dropwise addition of 25 ml (0.22 mol) 30% H₂O₂ and 50 ml of water. The mixture was refluxed for 4 hours, cooled and filtered. The filtrate was acidified with 1N HCl and the resulting precipitate recovered by filtration. The residue was recrystallized from MeOH to give 8.3 g (0.036 mol) of pale brown fluffy crystals. 36% yield. ¹H-NMR (CDCl₃): 1.10 (t, 3H, J=7.4Hz), 1.93 (m, 2H), 2.79 (3 line m; 2H, J=7.3Hz), 7.80 (d, 1H; J=8.9Hz), 8.55 (dd, 1H, J=2.5, 8.8Hz), 9.14 (bs, 1H).

PREPARATION OF 3N-ALKYL-2-ALKYLQUINAZOLIN-4(3H)-ONES

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A general procedure for the synthesis of 3-N-alkylated-quinazolin-4(3H)-ones is given below. Chromatography conditions, yields, and spectral data are given for the compounds prepared by this procedure.

A suspension of 1.1 mmol of NaH in 2 mL of dry PMF at 0°C under nitrogen was treated with 1 mmol of the quinazolin-4(1H)-one as a solid (most quinazolin-4(1H)-ones prepared were insoluble in DMF). 40 Immediate evolution of hydrogen could be observed as the quinazolin-4(1H)-one was deprotonated and dissolved. After 30 minutes the solution was warmed to room temperature for a further 30 minutes. To this solution cooled to 0°C was added a solution of 1 mmol of either 4-bromomethyl-2'-t-butoxycarbonyl-biphenyl, 4-bromomethyl-2'-cyano-biphenyl or N-triphenylmethyl-5-[2-(4'-bromomethylbiphenyl)] tetrazole in 1.5 mL of DNF. After 30 minutes, the reaction mixture was warmed to room temperature and stirred 45 overnight. The solution was concentrated in vacuo, and the residue dissolved in 50 mL of EtAc. The solution was washed with water (3x10 mL) and brine (2x10 mL). The organic phase was dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified as indicated below:

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EXAMPLE 172-Butyl-3-[(2'--(t-butoxycarbonyl)biphen-4-yl)-methyl]quinazolin-4(3H)-one

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The quinazolinone prepared as described in Example 11 was alkylated with 4-bromomethyl-2'-t-butoxycarbonyl-biphenyl. The product was purified by flash chromatography over silica gel eluting with 1% EtAc/methylene chloride. ¹H-NMR (300 MHz, CDCl₃): 8.32 (m, 1H), 7.76 (m, 2H), 7.46 (m, 2H), 7.38 (m,

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1H), 7.32-7.18(m, 5H), 5.46 (bs, 2H), 2.79 (3 line m, 2H), 1.80 (m, 2H), 1.44 (m, 2H), 1.23 (s, 9H), 0.95 (t, 3H).

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EXAMPLE 18

2-Butyl-3-[(2'-(cyano)biphen-4-yl)methyl]quinazolin-4(3H)-one

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The quinazolinone prepared as described in Example 11 was alkylated with 4-bromomethyl-2'-cyanobiphenyl. The product was purified by MPLC Lobar C silica column eluting with 25% EtAc/hexane. R_f 0.13 in 30% EtAc/hexane. ¹H-NMR (300 MHz, CDCl₃): 8.32 (m, 1H), 7.84-7.59 (m, 7H), 5.46 (bs, 2H), 2.79 (3 line m, 2H), 1.80 (m, 2H), 1.44 (m, 2H), 0.94 (t, 3H).

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EXAMPLE 19

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2-Butyl-3-[(2'-(t-butoxycarbonyl)biphen-4-yl)-methyl]-8-methylquinazolin-4(3H)-one

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The quinazolinone prepared as described in Example 7 was alkylated with 4-bromomethyl-2'-t-butoxycarbonyl-biphenyl. The product was purified by flash chromatography over silica eluting 12.5% EtAc/hexane. 58% yield. ¹H-NMR (CDCl₃): 0.95 (t, 3H, J=7.3Hz), 1.23 (s, 9H), 1.44 (m, 2H), 1.85 (m, 2H), 2.62 (s, 3H), 2.79 (dd, 2H, J=7.65, 7.65Hz), 5.45 (bs, 2H), 7.20-7.50 (m, 8H), 7.59 (dd, 1H, J=1.1, 8.47Hz), 7.77 (dd, 1H, J=1.6, 7.7Hz), 8.16 (dd, 1H, J=1.2, 7.7Hz). FABMS, 483 (M⁺ +1).

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EXAMPLE 20

2-Butyl-3-[(2'-(t-butoxycarbonyl)biphen-4-yl)-methyl]-6-methylquinazolin-4(3H)-one

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The quinazolinone prepared as described in Example 1 was alkylated with 4-bromomethyl-2'-t-butoxycarbonyl-biphenyl. The product was purified by flash chromatography over silica gel eluting with 15% EtAc/hexane, 43% yield. ¹H-NMR (CDCl₃): 0.95 (t, 3H, J=7.3Hz), 1.23 (s, 9H), 1.43 (m, 2H), 1.79 (m, 2H), 2.49 (s, 3H), 2.77 (dd, 2H, J=8.0, 8.0Hz), 5.46 (bs, 1H), 7.19-7.60 (m, 10H), 7.77 (dd, 1H, J=1.6, 7.6Hz). FABMS, 483 (M⁺ +1).

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EXAMPLE 21

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2-Butyl-3-[(2'-(t-butoxycarbonyl)biphen-4-yl)-methyl]-6-nitroquinazolin-4(3H)-one

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The quinazolinone prepared as described in Example 10 was alkylated with 4-bromomethyl-2'-t-butoxycarbonyl-biphenyl. The product was purified by flash chromatography over silica gel eluting with 20% EtAc/hexane, 48% yield. ¹H-NMR (CDCl₃): 0.96 (t, 3H, J=7.38Hz), 1.25 (s, 9H), 1.45 (m, 2H), 1.83 (m, 2H), 2.84 (dd, 2H, J=8.08Hz), 5.47 (bs, 2H), 7.20-7.50 (m, 8H), 7.78 (d, 1H, J=9.07Hz), 8.53 (dd, 1H, J=2.5, 8.8Hz), 9.18 (d, 1H, J=2.5Hz). FABMS, m/z 514 (M⁺ +1).

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EXAMPLE 22

2-Butyl-3-[(2'-cyanobiphen-4-yl)-methyl]-6-methylquinazolin-4(3H)-one

5 The quinazolinone prepared as described in Example 1 was alkylated with 4-bromomethyl-2'-cyanobiphenyl. The product was purified by MPLC Lobar C silica gel column eluting with 20% EtAc/hexane, 61% yield. ¹H-NMR (CDCl₃): 0.92 (t, 3H, J=7.5Hz), 1.42 (m, 2H), 1.77 (m, 2H), 2.48 (s, 3H), 2.77 (dd, 1H, J=8.0, 8.0Hz), 5.46 (bs, 3H), 7.30 (d, 1H, J=7.9Hz), 7.40-7.65 (m, 7H), 7.74 (d, 1H, J=7.9Hz), 8.09 (s, 1H).

EXAMPLE 23

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2-Butyl-3-[(2'-t-butoxycarbonyl)biphen-4-yl)-methyl]-7-methylquinazolin-4(3H)-one

15 The quinazolinone prepared as described in Example 3 was alkylated with 4-bromomethyl-2'-t-butoxycarbonylbiphenyl. The product was purified by flash chromatography over silica eluting with 20% EtAc/hexane, 62% yield. ¹H-NMR (CDCl₃): 0.95 (t, 3H, J=7.33Hz), 1.23 (s, 9H), 1.42 (m, 2H), 1.79 (m, 2H), 2.50 (s, 3H), 2.77 (dd, 2H, J=7.9, 7.9Hz), 5.44 (bs, 2H), 7.20-7.51 (m, 9H), 7.76 (dd, 1H, J=1.31, 7.71Hz), 8.19 (d, 1H, J=8.13Hz). Anal (C₃₁H₃₄N₂O₃), C, H, N.

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EXAMPLE 24

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2-Butyl-3-[(2'-t-butoxycarbonyl)biphen-4-yl)-methyl]naphtho[2.3-e]quinazolin-4(3H)-one

30 The quinazolinone prepared as described in Example 4 was alkylated with 4-bromomethyl-2'-t-butoxycarbonyl-biphenyl. The product was purified by MPLC Lobar B silica gel column eluting with 15% EtAc/hexane, 3.6% yield (note: low yield due to inseparable side product in starting quinazoline). ¹H-NMR (CDCl₃): 0.97 (t, 3H, J=7.27Hz), 1.24 (s, 9H), 1.46 (m, 2H), 1.85 (m, 2H), 2.82 (dd, 2H, J=8.2, 8.2Hz), 5.49 (bs, 1H), 7.2-7.61 (m, 9H), 7.76 (d, 1H, J=7.1Hz), 7.97 (d, 1H, J=8.6Hz), 8.06 (d, 1H, J=7.9Hz), 8.17 (s, 1H), 8.94 (s, 1H).

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EXAMPLE 25

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2-Butyl-3-[(2'-t-butoxycarbonyl)biphen-4-yl)-methyl]-6,8-dimethylquinazolin-4(3H)-one

45 The quinazolinone prepared as described in Example 6 was alkylated with 4-bromomethyl-2'-t-butoxycarbonyl-biphenyl. The product was purified by MPLC Lobar B silica column eluting with 17% EtAc/hexane, 47% yield. ¹H-NMR (CDCl₃): 0.95 (t, 3H, J=7.2Hz), 1.23 (s, 9H), 1.42 (m, 2H), 1.83 (m, 2H), 2.43 (s, 3H), 2.58 (s, 3H), 2.77 (dd, 2H, J=7.7Hz), 5.44 (bs, 2H), 7.19-7.48 (m, 8H), 7.76 (d, 1H, J=6.2Hz), 7.95 (s, 1H).

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EXAMPLE 262-Propyl-3-[(2'-cyano)biphen-4-yl)methyl]-6-methylquinazolin-4(3H)-one

55 The quinazolinone prepared as described in Example 2 was alkylated with 4-bromomethyl-2'-cyanobiphenyl. The product was purified by MPLC Lobar C silica column eluting with 30% EtAc/hexane, 34% yield. ¹H-NMR (CDCl₃): 8.10 (s, 1H), 7.79-7.25 (m, 10H), 5.49 (bs, 2H), 2.76 (3 line m, 2H), 2.49 (s, 3H), 1.84 (m, 2H), 1.02 (t, 3H, J=7.4Hz).

EXAMPLE 275 2-Butyl-3-[2'-(t-butoxycarbonyl)biphen-4-yl-methyl]-5-methylquinazolin-4(3H)-one

The quinazolinone prepared as described in Example 5 was alkylated with 4-bromomethyl-2'-t-butoxycarbonyl-biphenyl. The product was purified by MPLC Lobar B silica column eluting with 17% EtAc/hexane. ¹H-NMR (CDCl₃): 0.95 (t, 3H, J = 7.3Hz), 1.22 (s, 9H), 1.43 (m, 2H), 1.79 (m, 2H), 2.76 (dd, 2H, J = 7.7, 7.7Hz), 2.87 (s, 3H), 5.40 (bs, 2H), 7.18-7.59 (m, 10H), 7.77 (dd, 1H, J = 1.4, 7.4Hz).

EXAMPLE 28

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6-Isopropyl-2-butyl-3-[2'-(N-triphenylmethyltetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one

The quinazolinone prepared as described in Example 8 was alkylated with N-triphenylmethyl-5-[2-(4'-bromomethylbiphenyl)] tetrazole in the same general manner as above. The product was purified by MPLC Lobar silica column to give a colorless oil, 51% yield. ¹H-NMR (CDCl₃): 0.89 (t, 3H, J = 7.27Hz), 1.33 (d, 6H, J = 6.9Hz), 1.34 (m, 2H), 1.71 (m, 2H), 2.66 (3 line m, 2H, J = 7.6Hz), 3.08 (m, 1H), 5.31 (bs, 2H), 6.90-7.51 (m, 23H), 7.65 (m, 1H), 7.93 (dd, 1H, J = 2.7, 7.0Hz), 8.17 (bs, 2H). FABMS m/z 721 (M⁺ + 1) calc. for C₄₈H₄₄N₈O.

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EXAMPLE 29

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6-Nitro-2-butyl-3-[2'-(N-triphenylmethyl-tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one

The quinazolinone prepared as described in Example 10 was alkylated with N-triphenylmethyl-5-[2-(4'-bromomethylbiphenyl)] tetrazole in the same general manner as above. The product was purified by flash chromatography over silica gel eluting with 50% CH₂Cl₂/hexanes and gradually increasing the proportion of EtAc to 15%, 37% yield. ¹H-NMR (CDCl₃ 300 MHz): 0.90 (t, 3H, J = 7.5Hz), 1.35 (m, 2H), 1.72 (m, 2H), 2.72 (3 line m, 2H, 7.9Hz), 5.31 (bs, 2H), 6.89-7.00 (m, 8H), 7.12 (d, 2H, J = 8.0Hz), 7.23-7.37 (m, 11H), 7.48 (m, 2H), 7.77 (d, 1H, J = 9.0Hz), 7.92 (m, 1H), 8.53 (dd, 1H, J = 2.7, 9.1Hz), 9.18 (d, 1H, J = 2.6Hz).

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EXAMPLE 30

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2-Butyl-3-[2'-(N-triphenylmethyl-tetrazol-5-yl)-biphen-4-yl)methyl]-6-thiomethylquinazolin-4(3H)-one

The product of Example 9 was alkylated with N-triphenylmethyl-5-[2-(4'-bromomethylbiphenyl)]-tetrazole following the general protocol described above. The product was purified by flash chromatography over silica gel eluting with 20%EtAC/hexane, 51% yield. ¹H-NMR (CDCl₃ 300 MHz): 0.89 (t, 3H), 1.33 (m, 2H), 1.71 (m, 2H), 2.58 (s, 3H), 2.62 (3 line m, 2H), 5.28 (bs, 2H), 6.85-6.98 (m, 8H), 7.08 (d, 2H), 7.18-7.36 (m, 10H), 7.43 (m, 2H), 7.60 (m, 2H), 7.91 (dd, 1H), 8.07 (d, 1H).

EXAMPLE 31

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2-Butyl-3-(4'-fluoro-2'-(N-triphenylmethyltetrazol-5-yl)biphen-4-yl)methyl-6-isopropylquinazolin-4(3H)-one

To a solution of 2-butyl-6-isopropylquinazolinone (55.6 mg; 0.228 mmol) (Example 8) in dry DMF (1.5 mL) was added NaH, 80% oil dispersion, (11.8 mg; 1.5 eq). The reaction mixture was allowed to stir for 30 min. under N₂. To this was added a solution of N-Triphenylmethyl-5-(4-fluoro-4'-bromomethyl-biphen-2-yl)-tetrazole (crude) in dry DMF (1.5 mL). The reaction was stirred under N₂ for 3 hrs. then quenched with 5 saturated NH₄Cl solution. The solvent was removed at high vacuum, replaced by EtOAc, and the insoluble salts filtered off. The product was purified by flash chromatography on a silica column eluting with Hex/EtOAc = (35:1) to afford 94.5 mg (56%) of the titled compound. Characteristic peaks ¹H NMR (300 MHz, CDCl₃) δ 0.87 (t, 3H), 1.30 (d, 6H), 1.68 (m, 2H), 2.63 (t, 2H), 3.05 (q; 1H), 5.28 (s, 2H), 8.13 (s, 1H).

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EXAMPLE 3215 2-Butyl-6-methyl-3-[(2'-nitrobiphen-4-yl)methyl]-quinazolinone

To a solution of 0.111 g (0.51 mmol) of 2-butyl-6-methylquinazolinone in 4.0 mL of dimethylformamide was added 0.022 g of a 60% oil dispersion of sodium hydride and the resulting mixture was stirred at room temperature under a nitrogen atmosphere. After 30 min hydrogen evolution had ceased, and 0.150 g (0.51 mmol) of 4-bromomethyl-2'-nitrobiphenyl was added to the reaction mixture. Stirring was continued for 2 h at room temperature and then the reaction mixture was partitioned between ethyl acetate and water. The organic layer was extracted, washed with water, brine, then dried (MgSO₄), filtered and evaporated. The residual oil was purified on a silica gel flash chromatography column eluted with 25% ethyl acetate-hexane to afford 0.129 g (59%) of the product as a colorless oil which had: NMR (CDCl₃) δ 0.91 (t, J = 10 Hz, 3H), 1.34-1.47 (m, 2H), 1.69-1.80 (m, 2H), 2.46 (s, 3H), 2.74 (t, J = 11 Hz, 2H), 5.43 (s, 2H), 7.18-7.28 (m, 4H), 7.36 (d, J = 12 Hz, 1H), 7.45 (t, J = 12 Hz, 1H), 7.52-7.62 (m, 3H), 7.83 (d, J = 12 Hz, 1H), 8.08 (s, 1H); MS (FAB) m/e 428 (MH⁺).

30

EXAMPLE 333-[(2'-Aminobiphen-4-yl)methyl]-2-butyl-6-methylquinazolin-4(3H)-one

35 To a solution of 0.127 g (0.30 mmol) of 2-butyl-6-methyl-3-[(2'-nitrobiphen-4-yl)-methyl]quinazolinone in from Example 32 15 mL of absolute ethanol was added 0.030 g of a 10% palladium on powdered charcoal catalyst and the resulting mixture was hydrogenated under a 35 psig hydrogen atmosphere in a Parr apparatus. After 1 h TLC analysis (50% ethyl acetate-hexane) of the reaction mixture indicated complete 40 reduction. The mixture was filtered, evaporated and dried in vacuo to afford 0.114 g (97%) of a viscous oil which was used directly in the next step without further purification: NMR (CDCl₃) δ 0.91 (t, J = 10 Hz, 3H), 1.36-1.47 (m, 2H), 1.70-1.82 (m, 2H), 2.47 (s, 3H), 2.77 (t, J = 11 Hz, 2H), 3.72 (br s, 2H), 5.44 (s, 2H), 6.70-6.83 (m, 2H), 7.04-7.16 (m, 2H), 7.23 (d, J = 14 Hz, 2H), 7.39 (d, J = 14 Hz, 2H), 7.56 (s, 2H), 8.08 (s, 1H); MS (FAB) m/e 398 (MH⁺).

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EXAMPLE 34

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2-Butyl-6-methyl-3-[(2'-trifluoromethylsulfonamidobiphen-4-yl)-methyl]quinazolin-4(3H)-one

To a solution of 0.114 g (0.29 mmol) of the product of Example 33 in 3.0 mL of dichloromethane was added 0.074 g (0.36 mmol) of 2,6-di-tert-butyl-4-methylpyridine and the reaction was stirred at room 55 temperature under a nitrogen atmosphere. Trifluoromethanesulfonic anhydride (0.101 g, 0.36 mmol) was added at once via syringe and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was then partitioned between dichloromethane and water and the organic layer was extracted. The organic layer was washed with 1.0 N hydrochloric acid, water, dried (MgSO₄), filtered and evaporated; The

residual oil was purified on a silica gel flash chromatography column eluted with 25% ethyl acetate-hexane. Evaporation of the purified fractions and drying in vacuo afforded 0.049 g (32%) of an off white amorphous solid which had: NMR (CDCl_3) δ 0.91 (t, $J=10$ Hz, 3H), 1.37-1.48 (m, 2H), 1.74-1.85 (m, 2H), 2.46 (s, 3H), 2.75 (t, $J=11$ Hz, 2H), 5.44 (s, 2H), 6.61 (br s, 1H), 7.21-7.32 (m, 7H), 7.54-7.64 (m, 3H), 8.08 (s, 1H); MS (FAB) m/e 530 (MH^+).

EXAMPLE 35

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6-Acetoxymethyl-2-butyl-3-[(2'-(N-triphenylmethyl)tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one

To a solution of 0.8 g (2.9 mmol) of the product of Example 14 in 30 mL of dry DMF at 0 °C was added 15 6.13 g (3.0 mmol) of a 0.5 M solution of potassium hexamethyl disilazide in toluene. The reaction mixture was stirred for 30 minutes and then treated with a solution of 1.54 g (3.0 mmol) of Ntriphenylmethyl-5-[2-(4'-bromomethylbiphenyl)] tetrazole in 6 mL of DMF. The reaction mixture was stirred for 6 hours while allowing the temperature to rise to 25 °C. The solution was taken up in 100 mL of EtAc and washed with water (3x20 mL) and brine (1x20 mL) and dried over Mg_2O_4 . The mixture was filtered and concentrated in 20 and the residue was purified by flash chromatography over silica eluting with 25% EtAOc/hexanes to give 0.71 g of a white foam, 33% yield. $^1\text{H-NMR}$ (CDCl_3): 0.89 (t, 3H, $J=7.3$ Hz), 1.32 (m, 2H), 1.71 (m, 2H), 2.13 (s, 3H), 2.66 (3 line m, 2H, 7.7 Hz), 5.23 (s, 2H), 5.30 (bs, 2H), 6.88-6.95 (m, 8H), 7.10 (d, 2H, $J=8.2$ Hz), 7.21-7.35 (m, 11H), 7.46 (m, 2H), 7.71 (m, 2H), 7.92 (m, 1H).

25

EXAMPLE 36A

30 5-Acetoxymethyl-2-butyl-3-[(2'-(N-triphenylmethyl)tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one

The product of Example 15 was alkylated with N-triphenylmethyl-5-[2-(4'-bromomethylbiphenyl)] tetrazole following the method described in Example to give a 57% yield of the title compound. $^1\text{H-NMR}$ (CDCl_3): 0.99 (t, 3H, $J=7.0$ Hz), 1.32 (m, 2H), 1.71 (m, 2H), 2.18 (s, 3H), 2.64 (3 line m, 2H, $J=7.3$ Hz), 5.25 (bs, 2H), 5.85 (s, 2H), 6.89-6.97 (m, 8H), 7.10 (d, 2H, 6.2 Hz), 7.22-7.35 (m, 11H), 7.45 (m, 2H), 7.68 (m, 2H), 7.92 (m, 1H).

EXAMPLE 36B

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2-Butyl-3-[2'-(t-butoxycarbonyl)biphen-4-yl]-methyl]-6-isopropylquinazolin-4(3H)-one

45 To a suspension of sodium hydride (0.034 g of 50% oil suspension) in dry DMF (5 mL) was added 2-n-butyl-6-isopropylquinazolin-4-one (prepared as described in Example 8) (0.2 g, 0.76 mMol) and stirred at room temperature for 1.5 hours. At this stage, 4-bromomethyl-2'-t-butoxycarbonylbiphenyl (0.29 g; 0.77 mMol) was added, and the mixture was stirred at room temperature for 18 hours. The crude product isolated, after work-up as described in the general procedure for alkylation of quinazolin-4(3H)-ones was 50 purified by flash chromatography over silica-gel using methylene chloride containing 1% methanol to give the desired compound as white amorphous solid (0.23 g, 67%). $^1\text{H-NMR}$ (CDCl_3): 0.97 (t, 3H; $J=7.35$ Hz), 1.19 (s, 9H), 1.31 (d, 6H, $J=6.9$ Hz, 1.45 (m, 2H), 1.81 (m, 2H, 2.95 (t, 2H, $J=7.7$ Hz), 3.07 (m, 1H), 5.69 (s, 2H), 7.33-7.94 (m, 11H). FAB-MS: m/e 455 ($M + H$), 909 (2 $M + H$).

55

ALTERNATIVE PREPARATION OF 2-BUTYL-3-[(2'-(N-TRIPHENYLMETHYL-TETRAZOL-YL)-BIPHEN-4-YL)-METHYL] ALKYL-QUINAZOLIN-4(3H)-ONES IN A SINGLE POT REACTION FROM ANTHRANILIC ACIDS

EXAMPLE 375 2-Butyl-7-chloro-3-[(2'-(Ntriphenylmethyl-tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one

To 0.17 g (1.0 mmol) of 2-amino-4-chlorobenzoic acid in 1 ml of dry pyridine under N_2 was added 0.24 g (2.0 mmol) of valeroyl chloride. The solution was heated for 5 hours. TLC (40% EtAc/hexanes indicated formation of a non polar intermediate. To this solution was added 0.45 g (1.0 mmol) of N-triphenylmethyl-5-[2-(4'-aminomethylbiphenyl)]tetrazole and the solution was heated at 120 °C overnight. The solution was taken up in 30 ml of EtAOc and 10 ml of water. The organic phase was washed with water (3x10 ml), sat. $NaHCO_3$ (2x10 ml) and sat. $NaCl$ (1x10 ml). The organic phase was dried over $MgSO_4$, filtered and concentrated in *vacuo*. The residue was purified by flash chromatography over silica eluting with 20% EtAOc/hexanes to give 0.153 g of an oil, 21% yield. 1H -NMR ($CDCl_3$): 0.89 (t, 3H, J = 7.4Hz), 1.32 (m, 2H), 1.69 (m, 2H), 2.65 (3 line m, 2H, J = 7.7Hz), 5.28 (bs, 2H), 6.83-7.50 (m, 23H), 7.69 (d, 1H, J = 1.95Hz), 7.92 (dd, 1H, J = 2.22, 6.78Hz), 8.23 (d, 1H, J = 8.52Hz). FABMS m/z 713 (N + 1) calc. for $C_{45}H_{37}N_6OCl$.

EXAMPLE 38

20

2-Butyl-6-ethyl-3-[(2'-(N-triphenylmethyl-tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one

25 As in the procedure described above for Example 37. Purification by flash chromatography eluting with 20% EtAOc/hexane to give a pale yellow oil, 16% yield. 1H -NMR ($CDCl_3$): 0.89 (t, 3H, J = 7.4Hz), 1.32 (t, 3H, J = 7.5Hz), 1.3-1.4 (m, 2H), 1.72 (m, 2H), 2.67 (3 line m, 2H), 2.80 (q, 2H, J = 7.5Hz), 5.32 (bs, 2H), 6.90-7.5 (m, 22H), 7.63 (s, 2H), 7.94 (dd, 1H, J = 1.5, 6.9Hz), 8.16 (bs, 1H).

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FURTHER TRANSFORMATIONS OF 3-N-ALKYL-QUINAZOLIN-4(3H)-ONES BEFORE REMOVAL OF PROTECTING GROUPS

35

EXAMPLE 396-Amino-2-butyl-3-[(2'-(t-butoxycarbonyl)biphen-4-yl)methyl]quinazolin-4(3H)-one

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0.11 g (0.21 mmol) of 2-butyl-3-[(2'-(t-butoxycarbonyl)biphen-4-yl)methyl]quinazolin-3(1H)-one (Example 21) was suspended in 7.5 mL of MeOH and hydrogenated over 55 mg of 10% Pd/C under an atmospheric pressure hydrogen blanket. After 1 hour the reaction mixture was filtered through celite and the filtrate concentrated in *vacuo*. The residue was purified by flash chromatography over silica gel eluting with 50% EtAOc/hexane to give 69 mg (0.14 mmol) of a white foam, 67% yield. 1H -NMR ($CDCl_3$): 0.94 (t, 3H, J = 7.7Hz), 1.23 (s, 9H), 1.41 (m, 2H), 1.79 (m, 2H), 2.74 (3 line m, 2H, J = 7.7Hz), 5.44 (bs, 2H), 7.05-7.57 (m, 10H), 7.77 (d, J = 7.5Hz).

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EXAMPLE 406-Amino-2-butyl-3-[(2'-(N-triphenylmethyl-tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one

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A solution of 3.2 g (4.4 mmol) of the 6-nitroquinazolinone from Example 28 in 100 mL of EtAOc was hydrogenated over night under atmospheric pressure in the presence of 0.5 g of 10% Pd/C. The solution was filtered through celite and the celite was washed with CH_2Cl_2 to remove any of the yellow coloured

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product. The filtrate was concentrated in to give 3.0 g of a pale yellow solid. The material was not purified further, 98% yield. ¹H-NMR (CDCl₃ 300MHz): 0.89 (t, 3H, J=7.3Hz), 1.32 (m, 2H), 1.69 (m, 2H), 2.62 (3 line m, 2H, J=7.9Hz), 4.00 (bs, 2H), 5.29 (bs, 2H), 6.88-7.02 (m, 6H), 7.08-7.15 (m, 4H), 7.22-7.38 (m, 11H), 7.45-7.55 (m, 4H), 7.93 (dd, 1H, J=2.5, 7.0Hz).

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EXAMPLE 41

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6-Amino-2-propyl-3-[(2'-(N-triphenylmethyl-tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one

The product of Example 32 was hydrogenated as described in Example 40. The product was purified by flash chromatography over silica gel eluting with 7% Acetone/CH₂Cl₂ to give a pale yellow solid. 72% yield. ¹H-NMR (CDCl₃): 0.92 (m, 3H, J=7.4Hz), 1.72 (m, 2H), 2.58 (3 line m, 2H, J=7.7Hz), 5.56 (bs, 2H), 6.82-7.51 (m, 25H), 7.92 (dd, 1H, J=6.9, 1.9Hz).

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EXAMPLE 42

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6-Acetamido-2-butyl-3-[(2'-(N-triphenylmethyl-tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one

25 To a solution of 0.12 g (0.17 mmol) of the aminoquinazolinone from Example 40 in 2 mL of CH₂Cl₂ was added 33 mg (0.32 mmol) of triethyl amine followed by 10 mg of dimethylaminopyridine. The reaction mixture was cooled to 0 °C and treated with 14 mg (0.19 mmol) of acetyl chloride. The solution was allowed to warm to room temperature at which time a further 0.3 equivalents of acetyl chloride was added and the mixture was stirred overnight. The reaction mixture was concentrated in vacuo and the residue was purified by flash chromatography over silica gel eluting with 50% EtAc/hexanes containing a gradually increasing concentration of CH₂Cl₂ to 10% to give 0.073 g of the title compound, 57% yield. ¹H-NMR (CDCl₃ 250MHz): 0.88 (t, 3H, J=7.08 Hz), 1.32 (m, 2H), 1.70 (m, 2H), 2.19 (s, 3H), 2.64 (3 line m, 2H, J=7.2Hz), 5.30 (bs, 2H), 6.89-6.98 (m, 8H), 7.09 (d, 2H, J=8.1Hz), 7.20-7.35 (m, 10H), 7.46 (m, 2H), 7.66 (d, 1H, J=8.8Hz), 7.73 (bs, 1H), 7.92 (m, 1H), 8.14 (d, 1H), 8.26 (dd, 1H, J=8.8, 2.3Hz).

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EXAMPLE 43

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2-Butyl-3-[(2'-(N-triphenylmethyl-tetrazol-5-yl)-biphen-4-yl)methyl]6valeroyleamidoquinazolin-4(3H)-one

The product of Example 40 was acylated with valeroyl chloride in the same manner as that described in Example 42. The product was purified by flash chromatography over silica gel eluting with 30% EtAc/hexanes and increasing the concentration of EtAc to 50% to give an oil, 65% yield. ¹H-NMR (CDCl₃ 300MHz): 0.87 (t, 3H, J=7.3Hz), 0.93 (t, 3H, J=7.3Hz), 1.25-1.45 (m, 4H), 1.72 (m, 4H), 2.38 (t, 2H, J=7.7Hz), 2.62 (3 line m, 2H, J=7.9Hz), 5.28 (bs, 2H), 6.91 (m, 8H), 7.08 (d, 2H, J=8.2Hz), 7.20-7.35 (m, 11H), 7.45 (m, 2H), 7.64 (d, 1H, J=8.9Hz), 7.73 (bs, 1H), 7.91 (dd, 1H, J=2.6, 6.9Hz), 8.12 (d, 1H, J=2.4Hz), 8.27 (bd, 1H, J=8.8Hz).

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EXAMPLE 44

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2-Butyl-6-(N-carbobenzyloxy)amino-3-[(2'-(N-triphenyl-methyl-tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one

To a suspension of 4 mg (0.12 mmol) of 80% NaH in oil in 1 mL of dry DMF under nitrogen was added at 0 °C a solution of 69 mg (0.1 mmol) of the 6-aminoquinazolinone from Example 40. A bright blue solution was formed. After 0.5 hours 18.8 mg (0.1 mmol) of benzylchloroformate was added via syringe. The blue colour rapidly dissipated and the reaction mixture was stirred for 3 hours while allowing the temperature to 5 rise to room temperature. The reaction mixture was concentrated in vacuo and the residue was dissolved in 25 mL of EtAc and 5 mL of water. The aqueous phase was extracted with EtAc (2x5 mL) and the combined organic phases were washed with water (1x5 mL) and brine (1x5 mL) and dried over MgSO₄. The mixture was filtered and concentrated in and the residue was purified by flash chromatography over silica gel eluting with 30% EtAc/hexane to give 51.7 mg (0.62 mmol), 62% yield of the Example 26 compounds. ¹H-NMR (CDCl₃ 330MHz): 0.88 (t, 3H, J=7.3Hz), 1.32 (m, 2H), 1.68 (m, 2H), 2.60 (3 line m, 2H, J=8.41Hz), 10 5.19 (s, 2H), 5.29 (bs, 2H), 6.90 (m, 8H), 7.09 (d, 1H, J=8.2Hz), 7.2-7.52 (m, 18H), 7.65 (d, 1H, J=8.8Hz), 7.91 (m, 1H), 8.19 (m, 2H).

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EXAMPLE 45

20 6-(N-Isopropylcarbamoyl)amino-2-propyl-3-[(2'-(N-triphenylmethyl-tetrazol-5-yl)biphen-4-yl)methyl]-quinazolin-4(3H)-one

The product of Example 41 was converted to the title compound in the same manner as that described in Example 51. The product was purified by MPLC over silica gel eluting with 65% EtAc/hexane to give a colorless oil, 72% yield. ¹H-NMR (CDCl₃): 0.91 (t, 3H, J=7.4Hz), 1.13 (d, 6H, J=6.4Hz), 1.73 (m, 2H), 2.58 25 (3 line m, 2H, J=7.8Hz), 3.98 (m, 1H), 4.79 (d, 1H, J=7.8Hz), 5.30 (bs, 2H), 6.89-7.98 (m, 10H), 7.10 (d, 2H, J=8.2Hz), 7.21-7.32 (m, 12H), 7.46 (m, 2H), 7.63 (d, 1H, J=8.9Hz), 7.92 (m, 2H), 8.15 (2.5, 8.8Hz).

30

EXAMPLE 46

35 2-Butyl-6-(N-carbobenzyloxy-N-methyl)amino-3-[(2'-(N-triphenylmethyl-tetrazol-5-yl)biphen-4-yl)methyl]-aminoquinazolin-4(3H)-one

To a suspension of 20 mg (0.65 mmol) of 80% NaH in mineral oil in 2 mL of dry DMF at 0 °C under nitrogen was added a solution of 0.49 g (0.59 mmol) of the product of Example 44 in 4 mL of DMF. A blue solution formed on consumption of the NaH. The reaction mixture was allowed to stir for 90 minutes at which time 0.04 mL (0.6 mmol) of methyl iodide was added. The ice bath was removed and the reaction 40 mixture was stirred for a further 45 minutes. To the reaction mixture was added 1 mL of water and the DMF was removed in vacuo. The residue was dissolved in 50 mL of EtAOc and the organic phase was washed with water (2x20 mL) and brine (1.20 mL). The mixture was dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by flash chromatography over silica gel eluting with 30% EtAOc/hexane to give 0.44 g (0.52 mmol) of an orange solid, 89% yield. ¹H-NMR (CDCl₃ 300MHz): 0.88 (t, 3H, J=7.3Hz), 1.32 (m, 2H), 1.69 (m, 2H), 2.65 (3 line m, 2H, J=8.2Hz), 3.40 (s, 3H), 5.19 (s, 2H), 5.29 (bs, 2H), 6.92 (m, 8H), 7.09 (d, 2H, J=8.1Hz) 7.2-7.37 (m, 15H), 7.46 (m, 2H), 7.62 (d, 1H), 7.72 (m, 1H), 7.91 (d, 1H), 8.12 (d, 1H).

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EXAMPLE 47

55 2-Propyl-6-(N-methyl-N-isobutyloxycarbonyl)amino-3-[(2'-(N-triphenylmethyl-tetrazol-5-yl)-biphen-4-yl)-methyl]quinazolin-4(3H)-one

To a suspension of 9.7 mg (0.32 mmol) of 80% NaH in oil in 0.5 mL of dry DMF was added at 0°C a solution of 0.2 g (0.29 mmol) of the product of Example 41 in 0.5 ml of DMF. The orange solution was

stirred for 30 minutes and was then treated with 40 mg (0.29 mmol) of isobutyl chloroformate. After 1 hour 0.37 ml of a 1 M solution hexamethyl disilazine in THF was added dropwise to the reaction mixture. A red solution was formed to which was added 0.58 mg (0.41 mmol) of iodomethane. The reaction mixture was allowed to stir over night and concentrated *in vacuo*. The residue was dissolved in 20 ml of EtAOc and 5 washed with water (2x5 ml) and brine (1.5 ml) and dried over MgSO₄. The solution was filtered and concentrated *in vacuo*. The residue was purified by MPLC over silica gel eluting with 30% EtAc in hexanes to give 0.132 g a colorless oil. 56% yield. ¹H-NMR (CDCl₃): 0.88 (d, 6H, J=6.8Hz), 0.94 (t, 3H, J=7.3 Hz), 1.73 (m, 2H), 1.91 (m, 1H), 2.63 (3 line m, 2H, J=7.9 Hz), 4.12 (d, 2H, J=7.21 Hz), 5.29 (bs, 2H), 6.90-6.97 (m, 8H), 7.09 (d, 2H, J=8.1 Hz), 7.22-7.35 (m, 10H), 7.46 (m, 2H), 7.64 (d, 1H, J=8.7 Hz), 7.73 (bm, 1H), 10 7.92 (dd, 1H, J=2.5, 7.0 Hz).

EXAMPLE 48A

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2-Propyl-6-(N-ethyl-N-isobutyloxycarbonyl)amino-3-[(2'-(N-triphenylmethyl-tetrazol-5-yl)-biphen-4-yl)methyl]-quinazolin-4(3H)-one

20 The product of Example 41 was acylated with isobutyl chloroformate and then alkylated with iodoethane in the manner described in Example 47 to give the title compound. ¹H-NMR (CDCl₃): 0.86 (d, 6H, J=6.5Hz), 0.94 (t, 3H, J=7.4 Hz), 1.20 (t, 3H, J=7.1Hz), 1.77 (m, 2H), 1.87 (m, 2H), 2.63 (3 line m, 2H, J=7.8 Hz), 3.83 (q, 2H, J=7.1 Hz), 3.90 (d, 2H, J=6.5 Hz), 5.29 (bs, 2H), 6.89-6.98 (m, 8H), 7.10 (d, 2H, J=8.1 Hz), 7.22-7.36 (m, 10H), 7.47 (m, 2H), 7.64 (m, 2H), 7.92 (dd, 1H, J=4.3,6.9 Hz), 8.12 (d, 1H, J=2.33 Hz).

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EXAMPLE 48B

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6-(N-Butyl-N-isobutyloxycarbonyl)-amino-2-propyl-3-[(2'-(N-triphenylmethyl-tetrazol-5-yl)-biphen-4-yl)-methyl]quinazolin-4(3H)-one

35 The product of Example 41 was acylated with isobutylchloroformate and then alkylated with butyl iodide in the manner described in Example 47 to give the title compound. 71% yield. ¹H-NMR (CDCl₃): 0.82-0.98 (m, 12H), 1.31 (m, 2H), 1.53 (m, 2H), 1.76 (m, 2H), 1.87 (m, 1H), 2.63 (3 line m, 2H, J=7.9Hz), 3.76 (t, 2H, J=7.6Hz), 3.89 (d, 2H, J=6.6Hz), 5.29 (bs, 2H), 6.89-6.98 (m, 10H), 7.10 (d, 2H, J=8.2Hz), 7.22-7.35 (m, 8H), 7.46 (m, 2H), 7.64 (m, 2H), 7.92 (dd, 1H, J=2.1, 6.7Hz), 8.11 (d, 1H, J=2.3Hz).

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EXAMPLE 49

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6-(N-Benzyl)amino-2-butyl-3-[(2'-(N-triphenylmethyltetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one

To 100 mg (0.14 mmol) of the amine from Example 40 in 2 mL of EtOH was added 16 mg (0.15 mmol) of benzaldehyde. The reaction mixture was heated to 60 °C for 1 hour, cooled to 0 °C and treated with 0.29 50 mL (0.29 mmol) of a 1M solution of NaCNBH₃ in THF. The reaction mixture was stirred overnight, concentrated *in vacuo*, and the residue partitioned between 25 mL of EtAOc and 15 mL of water. The phases were separated and the organic phase was washed with brine (1x25 mL) and dried over MgSO₄. The mixture was filtered and concentrated *in vacuo* and the residue was purified by flash chromatography over silica gel eluting with 25% EtAOc/hexanes to give 45 mg (0.06 mmol) of a yellow foam. ¹H-NMR (CDCl₃ 300MHz): 0.88 (t, 3H, J=7.4Hz), 1.31 (m, 2H), 1.66 (m, 2H), 2.61 (3 line m, 2H, J=7.8Hz), 4.32 (bs, 1H), 4.43 (bs, 2H), 5.28 (bs, 2H), 6.88 (m, 8H), 7.08 (m, 3H), 7.20-7.53 (m, 19H), 7.91 (d, 1H).

EXAMPLE5 2-Butyl-6-(N,N-dimethyl)amino-3-[(2'-(N-triphenylmethyl-tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one.

To 100 mg (0.138 mmol) of the nitro quinazolinone from Example 29 in 1 mL of EtAc and 1 mL of MeOH was added 300 mg of formalin followed by 25 mg of 10% Pd/C. The mixture was rapidly stirred 10 under hydrogen at atmospheric pressure overnight. The reaction mixture was filtered and concentrated in vacuo. The residue was purified by flash chromatography over silica gel eluting with 30% EtAOc/hexane to give 30 mg (0.04 mmol) of a white foam, 24% yield. ¹H-NMR (CDCl₃ 300MHz): 0.88 (t, 3H, J = 7.3Hz), 1.42 (m, 2H), 1.69 (m, 2H), 2.62 (3 line m, 2H, J = 7.9Hz), 3.07 (s, 6H), 5.30 (bs, 2H), 6.90-6.99 (m, 6H), 7.07 (d, 2H, J = 8.1Hz), 7.21-7.37 (m, 13H), 7.45 (m, 3H), 7.57 (d, 1H, J = 8.9Hz), 7.92 (m, 1H).

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EXAMPLE 5120 2-Butyl-6-(N-isopropylcarbamoyl)amino-3-[(2'-(N-triphenylmethyl-tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one

To solution of 0.069 g (0.1 mmol) of the aminoquinazolinone from Example 40 in 1 mL of CH₂Cl₂ was 25 added 12.7 mg (0.15 mmol) of isopropylisocyanate. The reaction mixture was stirred for 3 days. The mixture was diluted with 20 mL of EtAOc, washed with water (2x5mL), brine (1x5 mL) and dried over MgSO₄. The mixture was filtered and concentrated in vacuo and the residue was purified by MPLC over a silica Lobar B column eluting with 50% EtAOc/hexanes to give 59.5 mg (0.07 mmol) of an oil, 76% yield. ¹H-NMR (CDCl₃ 300MHz): 0.86 (t, 3H, J = 7.3Hz), 1.07 (d, 6H, J = 6.5Hz), 1.29 (m, 2H), 1.68 (m, 2H), 2.59 (3 line m, 2H, J = 7.06 Hz), 3.95 (m, 1H), 5.18 (d, 1H, J = 7.7Hz), 5.28 (bs, 2H), 7.12 (m, 6H), 7.07 (d, 2H), 7.19-7.32 (m, 11H), 7.43 (m, 2H), 7.57 (m, 2H), 7.90 (m, 2H), 8.13 (m, 1H).

35

EXAMPLE 526-Acetamido-2-butyl-3-[(2'-(t-butoxycarbonyl)biphen-4-yl)methyl]quinazolin-4(3H)-one

40 To 20 mg of the product of Example 39 in 0.75 mL of CH₂Cl₂ at room temperature was added 4.3 uL of acetic anhydride. After 6 hours a further 2 uL of acetic anhydride was added to the reaction mixture. The solution was allowed to stir for 7 days, diluted with 10 mL of EtAOc and washed with water (3x5 mL), brine (1x5 mL) and dried over MgSO₄. The solution was filtered and concentrated in vacuo to give 22 mg of a white solid, 100% yield. Attempted dissolution in EtAOc and CH₂Cl₂ for chromatography failed due to 45 insolubility. ¹H-NMR (CD₃OD): 0.65 (t, 3H, J = 7.3Hz), 0.91 (s, 9H), 1.12 (m, 2H), 1.48 (m, 2H), 1.87 (s, 3H), 2.63 (3 line m, 2H, J = 7.7Hz), 5.21 (bs, 2H), 6.92-7.39 (m, 10H), 7.67 (dd, 1H, J = 2.5, 8.8Hz), 8.19 (d, 1H, J = 2.5Hz). FABMS m/z 526 (M⁺ + 1) calc for C₃₂H₃₅N₃O₄.

50 SYNTHESIS OF 2-BUTYL-3-[(2'-(CARBOXYBIPHEN-4-YL)METHYL)-ALKYL]QUINAZOLIN-4(3H)-ONES

General procedure for the preparation of the carboxylic acids from the t-butyl esters is as follows:

To 1 mmol of the ester in 1 mL of dry CH₂Cl₂ at room temperature was added 0.5 mL of trifluoroacetic acid. The solution was stirred under N₂ over night and concentrated in vacuo. The residue was 55 reconcentrated in vacuo after dissolving the reaction product in a mixture of 0.5 mL of CH₂Cl₂ and 3 mL of toluene. The residue was allowed to dry in vacuo overnight. Any impurities were removed by flash chromatography.

EXAMPLE 535 6-Acetamido-2-butyl-3-[(2'-carboxy)biphen-4-yl)methyl]-quinazolin-4(3H)-one

The product of Example 52 was deprotected following the general procedure described above. Purification by flash chromatography eluting with 5:95:1 MeOH:CH₂Cl₂:HOAc to give a white solid. ¹H-NMR (CD₃OD): 0.61 (t, 3H, J = 7.43Hz), 1.12 (m, 2H), 1.42 (m, 2H), 1.86 (s, 3H), 2.52 (3 line m, 2H, J = 7.4Hz), 10 5.18 (bs, 2H), 6.85-7.22 (m, 8H), 7.19 (d, 1H, J = 7.3Hz), 7.46 (d, 1H, J = 7.3Hz), 7.69 (dd, 1H, J = 2.2,8.8Hz), 8.12 (d, 1H, J = 2.22Hz). FABMS m/z 470 (M⁺ + 1) calc for C₂₈H₂₇N₃O₄.

EXAMPLE 54

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6-Amino-2-butyl-3-[(2'-carboxy)biphen-4-yl)methyl]quinazolin-4(3H)-one

20 The product of Example 39 was deprotected following the general procedure described above. Purification by flash chromatography over silica gel eluting with 60:40:1 EtAc:hexane:acetic acid. The product is very insoluble when concentrated to give a white solid. ¹H-NMR (CDCl₃): 0.87 (t, 3H, J = 7.37Hz), 1.35 (m, 2H), 1.69 (m, 2H), 2.71 (3 line m, 2H, J = 6.9Hz), 3.2-4.5 (bs, 4H), 5.41 (bs, 2H), 7.05-7.59 (m, 10H), 7.54 (bs, 1H).

25

EXAMPLE 55

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2-Butyl-3-[(2'-carboxy)biphen-4-yl)methyl]quinazolin-4(3H)-one

The product of Example 17 was deprotected following the general procedure described above. The crude material was purified by flash chromatography eluting with 1:1:38:60 acetic acid/MeOH/hexane/methylene chloride. ¹H-NMR (CDCl₃): 9.60-8.50 (bs, 1H), 8.30 (m, 1H), 7.94 (m, 1H), 7.71 (m, 2H), 7.58 -7.37 (m, 3H), 7.32 (m, 3H), 7.19 (m, 2H), 5.45 (bs, 2H), 2.75 (3 line m, 2H), 1.67 (m, 2H), 1.34 (m, 2H), 0.84 (t, 3H). FABMS m/z 413 (M⁺ + 1).

40

EXAMPLE 562-Butyl-3-[(2'-carboxy)biphen-4-yl)methyl]-5-methylquinazolin-4(3H)-one

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The product of Example 27 was deprotected following the general procedure described above. The crude concentrated reaction mixture was homogeneous by TLC and NMR. ¹H-NMR (CDCl₃): 0.88 (t, 3H, J = 7.21), 1.43 (m, 2H), 1.69 (m, 2H), 2.87 (s, 3H), 3.13 (dd, 2H, J = 8.0, 8.0Hz), 5.46 (bs, 2H), 7.21-7.36 (m, 5H), 7.43 (d, 2H, J = 8.74Hz), 7.58 (t, 1H, J = 7.4Hz), 7.69-7.81 (m, 2H), 7.96 (d, 1H, J = 7.8Hz).

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EXAMPLE 57

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2-Butyl-3-[(2'-carboxy)biphen-4-yl)methyl]naphtho[2,3-e]quinazolin-4(3H)-one

The product of Example 24 was deprotected following the general procedure described above. The

crude concentrated reaction mixture was homogeneous by TLC and NMR. $^1\text{H-NMR}$ (CDCl_3): 0.91 (t, 3H, $J = 7.22\text{Hz}$), 1.49 (m, 2H), 1.75 (m, 2H), 3.20 (bdd, 2H, $J = 7.6, 7.6\text{Hz}$), 5.52 (bs, 2H), 7.20-7.35 (m, 5H), 7.42 (t, 1H, $J = 7.7\text{Hz}$), 7.55 (t, 1H, $J = 7.3\text{Hz}$), 7.68 (t, 1H, $J = 7.3\text{Hz}$), 7.77 (t, 1H, $J = 8.0\text{Hz}$), 7.94 (d, 1H, $J = 7.7\text{Hz}$), 8.07 (d, 2H, $J = 8.2\text{Hz}$), 8.93 (s, 1H), 11.99 (bs, 1H). FABMS: m/z 463 ($M^+ + 1$).

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EXAMPLE 58

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2-Butyl-3-[(2'-carboxy)biphen-4-yl)methyl]-7-methylquinazolin-4(3H)-one

The product of Example 23 was deprotected following the general procedure described above. The product was purified by flash chromatography over silica eluting with 40% EtAOc/hexane/1% acetic acid. $^1\text{H-NMR}$ (CDCl_3): 0.91 (t, 3H, $J = 7.3\text{ Hz}$), 1.42 (m, 2H), 1.71 (m, 2H), 2.54 (s, 3H), 3.01 (dd, 2H, $J = 7.8, 7.8\text{ Hz}$), 5.44 (bs, 2H), 7.10-7.45 (m, 8H), 7.54 (t, 1H, $J = 7.5\text{Hz}$), 7.69 (s, 1H), 7.93 (d, 1H, $J = 7.7\text{Hz}$), 8.19 (d, 1H, $J = 8.1\text{ Hz}$). FABMS: 427 ($M^+ + 1$).

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EXAMPLE 59

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2-Butyl-3-[(2'-carboxy)biphen-4-yl)methyl]-8-methylquinazolin-4(3H)-one

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The product of Example 19 was deprotected following the general procedure described above. The product was purified by flash chromatography over silica gel eluting with 25% EtAOc/75% hexane/1% acetic acid. $^1\text{H-NMR}$ (CDCl_3): 0.91 (t, 3H, $J = 7.3\text{Hz}$), 1.41 (m, 2H), 1.82 (m, 2H), 2.61 (s, 3H), 2.78 (dd, 2H, $J = 7.3, 7.3\text{ Hz}$), 5.44 (bs, 2H), 7.15-7.61 (m, 9H), 7.92 (d, 1H, $J = 7.3\text{ Hz}$), 8.15 (d, 1H, $J = 7.8\text{Hz}$). FABMS: 427 ($M^+ + 1$).

EXAMPLE 60

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2-Butyl-3-[(2'-carboxy)biphen-4-yl)methyl]-6-methylquinazolin-4(3H)-one

40

The product of Example 20 was deprotected following the general procedure described above. The product was purified by flash chromatography over silica gel eluting with 30% EtAOc/70% hexane/1% acetic acid. $^1\text{H-NMR}$ (CDCl_3): 0.89 (3H, t), 1.38 (m, 2H), 1.69 (m, 2H), 2.48 (s, 3H), 2.83 (dd, 2H), 5.41 (bs, 2H), 7.16 (d, 2H), 7.22-7.31 (m, 3H), 7.41 (t, 1H), 7.52 (t, 1H), 7.59 (m, 1H), 7.68 (d, 1H), 7.91 (d, 1H), 8.08 (s, 1H). FABMS: 427 ($M^+ + 1$).

45

EXAMPLE 61

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2-Butyl-3-[(2'-carboxy)biphen-4-yl)methyl]-6-nitroquinazolin-4(3H)-one

55

The product of Example 21 was deprotected following the general procedure described above. The product was purified by flash chromatography over silica gel eluting with 70:30:1 EtAOc:hexane:acetic acid, 80% yield. $^1\text{H-NMR}$ (CDCl_3): 0.91 (t, 3H, $J = 7.33\text{Hz}$), 1.41 (m, 2H), 1.79 (m, 2H), 2.84 (3 line m, 2H, $J = 7.98\text{Hz}$), 5.45 (bs, 2H), 7.18-7.32 (m, 5H), 7.42 (dd, 1H, $J = 7.7, 7.7\text{Hz}$), 7.55 (dd, 1H, $J = 6.4, 6.4\text{Hz}$), 7.77 (d, 1H, $J = 9.0\text{Hz}$), 7.92 (d, 1H, $J = 7.4\text{Hz}$), 8.51 (dd, 1H, $J = 2.6, 9.3\text{Hz}$), 9.15 (d, 1H, $J = 2.6\text{Hz}$). FABMS m/z 458 ($M^+ + 1$) calc. for $C_{26}H_{23}N_3O_5$.

EXAMPLE 62A5 2-Butyl-3-[(2'-carboxy)biphen-4-yl)methyl]-6,8-dimethylquinazolin-4(3H)-one

The product of Example 25 was deprotected following the general procedure described above. Purification by flash chromatography over silica gel eluting with 30% EtAOc/ hexanes/1% acetic acid. ¹H-NMR (CDCl₃): 0.90 (t, 3H, J = 7.3Hz), 1.40 (m, 2H), 1.80 (m, 2H), 2.43 (s, 3H), 2.57 (s, 3H), 2.77 (3 line m, 10 2H, J = 7.7Hz), 5.44 (bs, 2H), 7.17-7.42 (m, 7H), 7.53 (dt, 1H, 7.5, 1.4Hz), 7.90-7.95 (m, 2H). FABMS: 441 (M⁺ + 1) calc. for C₂₈H₂₈N₂O₃.

ALTERNATIVE METHOD OF PREPARING CARBOXYLIC ACIDS FROM t-BUTYL ESTERS

15

EXAMPLE 62B

20

2-Butyl-3-[(2'-carboxybiphen-4-yl)-methyl]-6-isopropylquinazolin-4(3H)-one

A solution of 2-n-butyl-3-[(2'-t-butoxycarbonyl)biphen-4-yl)-methyl]-6-isopropylquinazolin-4(3H)-one (0.198 g, 0.44 mMol) from Example 36B in a mixture of methylene chloride (3 ml) and anhydrous trifluoroacetic acid (3 ml) containing anisole (0.05 ml) was stirred at room temperature for 4 hours. The solvent was then removed under reduced pressure and the residue was triturated with dry ether to give the solid product, which was then collected by filtration and dried in vacuo over NaOH and P₂O₅ to give the desired product as the morio trifluoroacetate salt. ¹H-NMR(CDCl₃): 0.91 (t, 3H, J = 7.35Hz), 1.32 (d, 6H, J = 6.9Hz), 1.47 (m, 2H), 1.72 (m, 2H), 3.12 (m, 3H), 5.48 (s, 2H), 7.14-7.96 (m, 11H), 8.16 (d, 1H, J = 1.9Hz). FAB-MS: 30 m/e 399 (M + H).

SYNTHESIS OF 2-BUTYL-3-[(2'-(TETRAZOL-5-YL)BIPHEN-4-YL)METHYL]QUINAZOLIN-4(3H)-ONES FROM TRITYL PROTECTED INTERMEDIATES

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EXAMPLE 63

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2-Butyl-6-ethyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one

The protected tetrazole from Example 38 (0.116 g, 0.165 mmol), was stirred with 1 ml of a mixture of 1:1:1 HOAc:THF:H₂O at 90 °C for 2 hours and then 4 hours at room temperature. The reaction mixture was 45 concentrated in vacuo and the residue was purified by flash chromatography over silica gel eluting with 40:59:1 EtAOc:hexane:HOAc. Recovered 53.4 mg of a white powder, 69% yield. ¹H-NMR (CDCl₃): 0.93 (t, 3H), 1.28 (t, 3H), 1.43 (m, 2H), 1.79 (m, 2H), 2.72 (m, 4H), 5.38 (bs, 2H), 7.18 (bs, 8H), 7.38 (d, 1H), 7.55 (m, 4H), 8.04 (s, 1H), 8.12 (d, 1H).

50

EXAMPLE 6455 2-Butyl-7-chloro-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one

Prepared as in Example 63 from the product of Example 37. Purification by flash chromatography over silica gel eluting with 40:59:1 EtAOc:hexane:HOAc to give a white powder. ¹H-NMR (CDCl₃): 0.94 (t, 3H,

J=7.3Hz), 1.42 (m, 2H), 1.79 (m, 2H), 2.77 (3 line m, 2H, J=7.6Hz), 5.37 (bs, 2H), 7.17 (s, 4H), 7.40 (m, 2H), 7.58 (m, 2H), 7.68 (d, 1H, J=1.96Hz), 8.09 (dd, 1H, J=1.3, 7.4Hz), 8.15 (d, 1H, J=8.5Hz). FABMS m/z 471 (M⁺ + 1) calc. for C₂₆H₁₃N₆OCl.

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EXAMPLE 65

10 2-Butyl-6-isopropyl-3-[(2'-*(*tetrazol-5-*y*l*)*biphen-4-*y*l*)*methyl]quinazolin-4(3H)-one

Prepared as in Example 63 from the product of Example 28. Purification by flash chromatography over silica gel eluting with 40:59:1 EtAOc:hexane:HOAc to give a white powder. ¹H-NMR (CDCl₃): 0.92 (t, 3H, J=7.3Hz), 1.29 (d, 6H, J=6.9Hz), 1.42 (m, 2H), 1.76 (m, 2H), 2.75 (3 line m, 2H, J=8.2Hz), 3.03 (m, 1H), 5.38 (bs, 2H), 7.16 (bs, 4H), 7.38 (dd, 1H, J=1.6, 7.1Hz), 7.5-7.7 (m, 4H), 8.06 (bm, 2H). FABMS m/z 479 (M⁺ + 1) calc. for C₂₉H₃₀N₆O.

20 EXAMPLE 66

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6-Acetoxyethyl-2-butyl-3-[(2'-*(*tetrazol-5-*y*l*)*biphen-4-*y*l*)*methyl]quinazolin-4(3H)-one

25 The product of Example 35 was deprotected as in the method for Example 63. The product was purified by flash chromatography over silica gel eluting with 50:49:1 EtAOc:hexane:acetic acid to give a white powder, (92% yield). ¹H-NMR (CDCl₃): 0.90 (t, 3H, J=7.3 Hz), 1.39 (m, 2H), 1.73 (m, 2H), 2.11 (s, 3H), 2.74 (3 line m, 2H, J=7.7Hz), 5.17 (s, 2H), 5.35 (bs, 2H), 7.08 (m, 4H), 7.39 (dd, 1H), 7.45-7.72 (m, 5H), 7.94 (dd, 1H, J=6.13, 1.5Hz), 8.17 (d, 1H, J=1.8Hz). FABMS m/e: 509 (M⁺ + 1) calc. for C₂₉H₂₈N₆O₃.

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EXAMPLE 67

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5-Acetoxyethyl-2-butyl-3-[(2'-*(*tetrazol-5-*y*l*)*biphen-4-*y*l*)*methyl]quinazolin-4(3H)-one

40 The product of Example 36 was deprotected as in the method for Example 63. The product was purified by flash chromatography over silica gel eluting with 50:50:1 EtAOc:hexane:acetic acid to give a white powder, (78% yield). ¹H-NMR (CDCl₃ 300MHz): 0.94 (t, 3H, J=7.4Hz), 0.43 (m, 2H), 1.79 (m, 2H), 2.17 (2, 3H), 2.78 (3 line m, 2H, J=7.8 Hz), 5.34 (s, 2H), 5.78 (s, 2H), 7.17 (s, 4H), 7.38-7.75 (m, 6H), 8.09 (m, 2H). FABMS m/e: 509 (M⁺ + 1) calc. for C₂₉H₂₈N₆O₃.

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EXAMPLE 68

2-Butyl-6-nitro-3-[(2'-*(*tetrazol-5-*y*l*)*biphen-4-*y*l*)*methyl]quinazolin-4(3H)-one

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55 The product of Example 29 was deprotected as in the method described in Example 63. The product was purified by flash chromatography over silica gel eluting with 50:49:1 EtAOc:hexane:acetic acid, 98% yield. ¹H-NMR (CDCl₃ 300MHz): 9.01 (t, 3H, J=7.3Hz), 1.42 (m, 2H), 1.79 (m, 2H), 2.79 (3 line m, 2H, 7.8Hz), 5.36 (bs, 2H), 7.14 (s, 4H), 7.37 (dd, 1H, J=1.5, 7.6Hz), 7.52 (m, 2H), 7.73 (d, 1H, J=8.9Hz), 7.97 (dd, 1H, J=2.0, 7.5Hz), 8.48 (dd, 1H, J=9.0, 2.6Hz), 9.01 (d, 1H, J=2.6Hz). FABMS m/e: 482 (M⁺ + 1) calc. for C₂₆H₂₃N₇O₃.

EXAMPLE 695 6-Amino-2-butyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one

The product of Example 40 was deprotected as in the method for Example 63. The product was purified by flash chromatography over silica gel eluting with 95:5:0.1 CHCl₃:MeOH:NH₄OH to give a white solid, 68% yield. ¹H-NMR (CDCl₃ 300MHz): 0.91 (t, 3H, J=7.3Hz), 1.41 (m, 2H), 1.72 (m, 2H), 2.69 (3 line m, 2H, J=7.8Hz), 5.35 (bs, 2H), 7.13 (s, 4H), 7.35-7.61 (m, 6H), 8.08 (dd, 1H, J=8.9, 1.7Hz). FABMS m/e: 452 (M⁺ + 1) calc. for C₂₆H₂₅N₇O.

EXAMPLE 70

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6-(N-Benzyl)amino-2-butyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one

20 The product of Example 49 was deprotected in the manner described in Example 63. The product was purified by flash chromatography over silica gel eluting with 5:95:0.01 MeOH:CHCl₃:NH₄OH to give slightly impure product. The material was purified further by MPLC over silica Lobar A column eluting with 50:50:1 EtAOc:hexane:acetic acid. ¹H-NMR (CDCl₃ 300MHz): 0.92 (t, 3H, J=7.3Hz), 1.41 (m, 2H), 1.73 (m, 2H), 2.72 (3 line m, 2H, J=8.1Hz), 4.39 (s, 2H), 5.35 (bs, 2H), 7.09 (dd, 1H, J=2.7, 8.8Hz), 7.13 (s, 3H), 7.23-26 7.40 (m, 8H), 7.43-7.60 (m, 3H), 8.09 (dd, 1H). FABMS m/e: 542 (M⁺ + 1) calc. for C₃₃H₃₁N₇O.

EXAMPLE 71

30

2-Butyl-6-(N,N-dimethyl)amino-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one

The product of Example 50 was deprotected in the manner described in Example 63. The product was purified by flash chromatography over silica gel eluting with 5% MeOH/CHCl₃, 95% yield. ¹H-NMR (CDCl₃ 300MHz): 0.92 (t, 3H, J=7.4Hz), 1.42 (m, 2H), 1.75 (m, 2H), 2.71 (3 line m, 2H, J=8.2 Hz), 3.03 (s, 6H), 5.36 (bs, 2H), 7.12 (s, 4H), 7.21 (dd, 1H, J=2.9, 9.0Hz), 7.31 (d, 1H, J=3.0Hz), 7.37 (m, 1H), 7.52 (m, 1H), 8.07, (dd, 1H, J=1.3, 7.2Hz). FABMS m/e: 480 (M⁺ + 1) calc. for C₂₈H₂₉N₇O.

40

AN ALTERNATIVE METHOD OF DEPROTECTING THE TRITYL GROUP:EXAMPLE 72

45

6-Acetamido-2-butyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one

50 To a solution of 0.073 g (0.099 mmol) of the product from Example 42 in 2 mL of MeOH was added 4 drops of conc. HCl. The reaction mixture was stirred for 5 minutes and then made basic by addition of conc. NH₄OH. The pH of the solution was adjusted to 5.0 by addition of the acetic acid. The reaction mixture was concentrated in vacuo and the residue was taken up in 20 ml of EtAOc. The solution was washed with water (2x5 mL) and brine (1x5 mL) and dried over MgSO₄. The mixture was filtered and concentrated in vacuo. The crude product was very insoluble and was consequently purified by trituration with CHCl₃, EtAOc and hexanes to give 32 mg of an off white solid, 65% yield. ¹H-NMR (CD₃OD 300MHz): 0.83 (t, 3H, J=7.3Hz), 1.32 (m, 2H), 1.62 (2H, m), 2.09 (s, 2H), 2.68 (3 line m, 2H, J=8.1Hz), 5.37 (bs, 2H), 7.00-7.10 (m, 4H), 7.42-7.61 (m, 5H), 7.89 (dd, 1H, J=2.4, 8.8Hz), 8.39 (d, J=2.5Hz). FABMS m/e: 494-

(M⁺ + 1) calc. for C₂₈H₂₇N₇O₂.

EXAMPLE 73

5

2-Butyl-3-[(2'-{(tetrazol-5-yl)biphen-4-yl)methyl}]6-valeroylamidoquinazolin-4(3H)-one

10 The product of Example 43 was deprotected in the manner of Example 72. The crude product was purified by trituration with a mixture of EtAOc and hexanes to give a powder, 78% yield. ¹H-NMR (CDCl₃ 300MHz): 0.91 (t, 3H, J = 7.4Hz), 0.97 (t, 3H, J = 7.3Hz), 1.41 (m, 4H), 1.70 (m, 4H), 2.42 (t, 2H, J = 7.6Hz), 2.75 (3 line m, 2H), 5.46 (bs, 2H), 7.12 (m, 4H), 7.51-7.69 (m, 5H), 7.99 (dd, 1H), 8.48 (d, 1H).

15

EXAMPLE 74

2-Butyl-6-(N-carbobenzyloxy-N-methyl)amino-3-[(2'-{(tetrazol-5-yl)biphen-4-yl)methyl}]quinazolin-4(3H)-one

20 The product of Example 46 was deprotected in the manner described in Example 72. The product was purified by MPLC over a silica Lobar A column eluting with 40:59:1 EtAOc:hexane:acetic acid to give a white foam, 87% yield. ¹H-NMR (CDCl₃ 300MHz): 0.91 (t, 3H, J = 7.4Hz), 1.40 (m, 2H), 1.72 (m, 2H), 2.73 (3 line m, 2H, J = 7.9Hz), 3.37 (s, 3H), 5.17 (s, 2H), 5.34 (bs, 2H), 7.10 (s, 4H), 7.31 (s, 4H), 7.37 (m, 1H), 7.47-7.61 (m, 4H), 7.69 (bd, 1H), 7.96 (dd, 1H, J = 1.3, 7.5Hz), 8.03 (d, 1H, H = 2.5Hz). FABMS m/e: 600 (M⁺ + 1) calc. for C₃₅H₃₃N₇O₃.

30

EXAMPLE 75

2-Butyl-6-(N-carbobenzyloxy)amino-3-[(2'-{(tetrazol-5-yl)biphen-4-yl)methyl}]quinazolin-4(3H)-one

35

35 The product of Example 45 was deprotected in the manner described in Example 72. The product was purified by MPLC over a silica Lobar A column eluting with 40:59:1 EtAOc:hexane:acetic acid to give a 55% yield of a white solid. ¹H-NMR (CDCl₃ 300MHz): 0.87 (t, 3H, J = 7.4Hz), 1.32 (m, 2H), 1.69 (m, 2H), 2.65 (3 line m, 2H, J = 7.3Hz), 5.15 (s, 2H), 5.29 (bs, 2H), 6.95 and 7.04 (AB, 4H, J = 8.2Hz), 7.30-7.42 (m, 5H), 7.49-7.59 (m, 3H), 7.72 (bs, 1H), 7.98 (d, 1H), 8.06 (s, 1H), 8.12 (bd, 1H). FABMS m/e: 586 (M⁺ + 1) calc. for C₃₄H₃₁N₇O₃.

45

EXAMPLE 76

2-Butyl-6-(N-isopropylcarbamoyl)amino-3-[(2'-{(tetrazol-5-yl)biphen-4-yl)methyl}]quinazolin-4(3H)-one

50 The product of Example 51 was deprotected following the procedure of Example 72. The product was purified by trituration with EtAOc and hexanes. ¹H-NMR (CD₃OD 300MHz): 0.82 (t, 3H, J = 7.4Hz), 1.10 (d, 6H, J = 6.6Hz), 1.29 (m, 2H), 1.40 (m, 2H), 2.65 (3 line m, 2H, J = 7.9Hz), 5.32 (bs, 2H), 6.99 (bs, 4H), 7.38 (m, 2H), 7.49 (m, 3H), 7.79 (dd, 1H, J = 2.5, 8.8Hz), 8.06 (d, 1H, J = 2.5Hz). FABMS m/e: 537 (M⁺ + 1) calc. for C₃₀H₃₂N₈O₂

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EXAMPLE 77

2-Butyl-3-[(2'-tetrazol-5-yl)biphen-4-yl)methyl]-6-thiomethylquinazolin-4(3H)-one

The product of Example 30 was deprotected in the same manner as that described in Example 72. The crude product was purified by flash chromatography over silica gel eluting with 50:49:1 EtAOc:hexane:acetic acid, 83% yield. ¹H-NMR (CDCl₃ 300MHz): 0.93 (t, 3H, J=7.4Hz), 1.43 (m, 2H), 1.78 (m, 2H), 2.55 (s, 3H), 2.76 (3 line m, 2H, J=7.9Hz), 5.38 (bs, 2H), 7.26 (s, 4H), 7.39 (dd, 1H, J=1.6,7.2Hz), 7.50-7.62 (m, 4H), 7.97 (d, 1H, J=2.1Hz), 8.07 (dd, 1H, J=1.3, 7.5Hz). FABMS m/e: 483 (M⁺ + 1) calc. for C₂₇H₂₆N₆SO

10

EXAMPLE 786-(N-Isopropylcarbamoyl)amino-2-propyl-3-[(2'-tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one

15

The product of Example 45 was deprotected in the manner described in Example 72. The product was purified by trituration with EtAOc to give a white solid. 62% yield. ¹H-NMR (CD₃OD): 0.88 (t, 3H, J=7.4Hz), 1.11 (d, 6H, J=6.6Hz), 1.63 (m, 2H), 2.64 (3 line m, 2H, J=7.9Hz), 3.82 (m, 1H), 5.34 (bs, 2H), 7.01 (s, 4H), 7.38-7.53 (m, 7H), 7.79 (dd, 1H, J=2.6, 8.9Hz).

20

EXAMPLE 79

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6-(N-Methyl-N-isobutyloxycarbonyl)amino-2-propyl-3-[(2'-tetrazol-4-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one

30

The product of Example 47 was deprotected in the manner described in Example 72. The product was purified by flash chromatography over silica gel eluting with 50% EtAOc in hexanes + 1% acetic acid to give a white solid. ¹H-NMR (CDCl₃): 0.88 (d, 6H, J=6.6 Hz), 0.99 (t, 3H, J=7.3 Hz), 1.80 (m, 2H), 1.90 (m, 1H), 2.71 (3 line m, 2H, J=7.8 Hz), 3.35 (s, 3H), 3.89 (d, 2H, J=6.6 Hz), 5.34 (bs, 2H), 7.09 (s, 4H), 7.12-7.39 (m, 2H), 7.46-7.61 (m, 3H), 7.79 (bd, 1H, J=8.2 Hz), 7.95 (d, 1H, J=6.8 Hz), 8.01 (d, 1H, J=2.3 Hz).

35

EXAMPLE 80A

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6-(N-Ethyl-N-isobutyloxycarbonyl)amino-2-propyl-3-[(2'-tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one

45

The product of Example 48A was deprotected by following the procedure outlined in Example 72. The product was purified by flash chromatography over silica gel eluting with 50% EtAOc/hexanes + 1% acetic acid. ¹H-NMR (CDCl₃): 0.86 (d, 6H, J=6.4Hz), 1.02 (t, 3H, J=7.4Hz), 1.17 (t, 3H, J=7.1Hz), 1.82 (m, 3H), 2.74 (3 line m, J=7.7Hz), 3.77 (q, 2H, J=7.06Hz), 3.88 (d, 2H, J=6.6Hz), 5.37 (bs, 2H), 7.16 (d, 2H, J=2.2Hz), 7.22-7.31 (m, 2H), 7.35-7.46 (m, 3H), 7.49-7.62 (m, 3H), 8.03 (m, 2H).

50

EXAMPLE 80B

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6-(N-Butyl-N-isobutyloxycarbonyl)-amino-2-propyl-3-[(2'-tetrazol-5-yl)-biphen-4-yl)methyl]quinazolin-4(3H)-one

The product of Example 48B was deprotected in the manner described in Example 72. The product was purified by flash chromatography over silica gel eluting with 40:60:1 EtAOc:hexanes:acetic acid to give

a white solid. 69% yield. $^1\text{H-NMR}$ (CDCl_3): 0.87 (m, 9H), 1.00 (t, 3H, $J=7.4\text{Hz}$), 1.29 (m, 2H), 1.52 (m, 2H), 1.75-1.91 (m, 3H), 2.72 (3 line m, 2H, $J=7.9\text{Hz}$), 3.72 (t, 2H, $J=7.4\text{Hz}$), 3.86 (d, 2H, $J=6.6\text{Hz}$), 5.35 (bs, 2H), 7.11 (s, 4H), 7.18 (m, 1H), 7.25 (m, 1H), 7.40 (d, 1H, $J=1.41\text{Hz}$), 7.49-7.58 (m, 7H), 7.94 (dd, 1H, $J=1.4, 7.5\text{Hz}$), 8.02 (d, 1H, $J=1.6\text{Hz}$).

5

EXAMPLE 81

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2-Butyl-6-(N-methyl-N-isobutyloxycarbonyl)amino-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one

The product of Example 95 was deprotected in the manner described in Example 72. The product was purified by flash chromatography over silica gel eluting with 50% $\text{EtAcO}/\text{hexanes} + 1\%$ acetic acid to give a white solid. $^1\text{H-NMR}$ (CDCl_3): 0.90 (m, 9H), 1.39 (m, 2H), 1.72 (m, 2H), 1.90 (m, 1H), 2.71 (3 line m, 2H, $J=7.5\text{Hz}$), 3.34 (s, 3H), 3.88 (d, 2H, $J=6.6\text{Hz}$), 5.32 (bs, 2H), 7.07 (s, 4H), 7.12-7.58 (m, 5H), 7.67 (m, 1H), 7.89 (dd, 1H, $J=1.5, 7.6\text{Hz}$), 8.00 (d, 1H, $J=2.5\text{Hz}$).

20

EXAMPLE 82

25

2-Butyl-3-(4'-fluoro-2'-(tetrazol-5-yl)biphen-4-yl)methyl-6-isopropylquinazolin-4(3H)-one

To a solution of 2-butyl-3-(4'-fluoro-2'-(N-triphenyl-methyltetrazol-5-yl)biphen-4-yl)methyl-6-isopropyl-quinazolinone from Example 33 (94.5 mg; 0.128 mmol) in MeOH (4 mL) was added 9 N HCl (10 drops). The reaction was allowed to stir overnight. After ca. 15 hrs. the MeOH was removed in vacuo. The product was purified by trituration with Et_2O to afford 54.2 mg (80%) of the titled compound. Characteristic peaks $^1\text{H-NMR}$ (300MHz, CD_3OD) d 0.86 (t, 3H), 1.38 (d, 6H), 1.52 (m, 2H), 1.69 (m, 2H), 3.08 (t, 2H), 3.20 (m, 1H), 5.60 (s, 2H), 7.19 (d, 2H), 7.33 (d, 2H), 7.74 (d, 1H), 8.00 (dd, 1H), 8.25 (d, 1H); mass spectrum, m/e 497 (m + H calcd for $\text{C}_{29}\text{H}_{29}\text{N}_6\text{OF}$, 497).

35

SYNTHESIS OF 2-BUTYL-3-[(2'-(TETRAZOL-5-YL)BIPHEN-4-YL)METHYL]QUINAZOLIN-4(3H)-ONES FROM NITRILES

40

General procedure for the conversion of the biphenyl nitrile to tetrazole is described below:

To a solution of 0.28 mmol of the nitrile dissolved in 2 mL of dry toluene was added 0.56 mmol of trimethylstannyl azide (see prior section for preparation). The reaction mixture was refluxed over night, at which time a further 0.56 mmol of azide was added and the reaction mixture refluxed a further 12 hours. The resulting suspension was suspended in 50 mL of EtAOc and washed with sat. NH_4Cl (3x10 mL) and dried over MgSO_4 . The solution was filtered and concentrated in vacuo. The method of purification and spectral data is shown below.

45

EXAMPLE 83

50

2-Butyl-6-methyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one

The product of Example 22 was treated as in the general method above. The residue was purified by flash chromatography over silica gel eluting 60% $\text{EtAOc}/\text{hexane}/1\%$ acetic acid to give 0.08 mmol of pure tetrazole, 32% yield. $^1\text{H-NMR}$ (CDCl_3): 0.92 (t, 3H, $J=7.3\text{Hz}$), 1.42 (m, 2H), 1.75 (m, 2H), 2.46 (s, 3H), 2.74 (3 line m, 2H, $J=7.9\text{Hz}$), 5.37 (bs, 2H), 7.11 (bs, 4H), 7.39 (m, 1H), 7.55 (m, 4H), 8.00 (m, 1H). FABMS m/z 451 ($\text{M}^+ + 1$) calc. for $\text{C}_{27}\text{H}_{26}\text{N}_6\text{O}$

EXAMPLE 845 2-Butyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one

The product of Example 18 was treated as in the general method above. The residue was purified by MPLC over silica gel eluting with 1:40:59 acetic acid: EtAOc: hexanes. The recovered product (R_f 0.27 in 1:39:60 acetic acid:EtAOc:hexanes) was further purified by HPLC on a C8 reverse phase column eluting with 75:25 acetonitrile:water/0.01% TFA to give the product as a white foam, 26% yield. $^1\text{H-NMR}$ (300MHz, CDCl_3): 11.50-10.30 (bs, 1H), 8.35 (m, 1H), 7.90 (m, 2H), 7.71 (m, 2H), 7.53 (m, 1H) 7.44 (m, 1H), 7.34 (M, 1h), 7.12 (m, 4H), 5.45 (bs, 2H), 3.17 (3 line m, 2H), 1.82 (m, 2H), 1.50 (m, 2H), 0.95 (t, 3H). FABMS m/z 437 ($M^+ + 1$).

16

EXAMPLE 8520 6-Methyl-2-propyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one

The product of Example 26 was treated as in the general method above. The crude tetrazole was purified in the same manner as in the 2-butyl case above, 13% yield. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 8.11 (m, 1H), 8.02 (s, 1H), 7.56 (m, 4H), 7.40 (m, 1H), 7.19 (m, 4H), 5.40 (bs, 2H), 2.73 (3 line m, 2H), 2.47 (s, 3H), 25 1.83 (m, 2H), 1.02 (t, 3H). FABMS m/z 437 ($M^+ + 1$). pKa 4.7.

FURTHER TRANSFORMATIONS OF ANTAGONISTS

30

EXAMPLE 8635 2-Butyl-6-hydroxymethyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one

A solution of 0.2 g (0.38 mmol) of the product of Example 66 was dissolved in 5 mL of MeOH and was treated with 1 mL of 1N NaOH (1.0 mmol) and stirred over night. The resulting solution was extracted with EtAOc (3x10 mL). The organic phase was washed with water (2x5 mL) and brine (1x5mL) and dried over 40 MgSO_4 . The mixture was filtered and concentrated in vacuo and the residue was purified by flash chromatography over silica gel eluting with 80:19:1 EtAOc:hexane:acetic acid to give 0.17 g (0.36 mmol) of a white foam, 93% yield. $^1\text{H-NMR}$ (CD_3OD): 0.88 (t, 3H, J = 7.38Hz), 1.41 (m, 2H), 1.48 (m, 2H), 2.73 (3 line m, 2H, J = 8.03Hz), 4.60 (s, 2H), 5.38 (bs, 2H), 7.08 (m, 4H), 7.20 (m, 1H), 7.50 (m, 2H), 7.61 (m, 2H), 7.77 (dd, 1H, J = 2.0, 9.0 Hz), 8.17 (s, 1H). FABMS m/e: 467 ($M^+ + 1$) calc. for $\text{C}_{27}\text{H}_{26}\text{N}_6\text{O}_2$

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EXAMPLE 87

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2-Butyl-5-hydroxymethyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one

To a solution of 0.2 g (273 mmol) of the product of Example 31 in 8 mL of MeOH was added 20 drops of conc. HCl. The reaction mixture was stirred overnight and the pH was then adjusted to pH 6.0. The 55 MeOH was removed in vacuo and the residue was triturated with 3 mL of EtAOc to give, after drying, 90 mg (1.9 mmol) of a white powder, 71% yield. $^1\text{H-NMR}$ (CD_3OD): 0.92 (t, 3H, J = 7.38 Hz), 1.40 (m, 2H), 1.72 (m, 2H), 2.76 (3 line m, 2H, J = 8.08 Hz), 5.16 (s, 2H), 5.44 (bs, 2H), 7.13 (m, 4H), 7.52-7.71 (m, 6H), 7.86 (t, 1H, J = 7.81Hz). FABMS m/e: 467 ($M^+ + 1$) calc. for $\text{C}_{27}\text{H}_{26}\text{N}_6\text{O}_2$

EXAMPLE 885 2-Butyl-6-carboxy-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one

To a solution of 115 mg (0.25 mmol) of the product of Example 86 in 6 mL of CH_2Cl_2 was added 600 mg of MnO_2 followed by 200 mg of 3A° molecular sieves. The reaction mixture was stirred for 12 hours and then filtered through celite. The celite was washed with CH_2Cl_2 (20 mL) and the combined filtrates 10 were concentrated in vacuo to give 65 mg of a white foam. 31 mg (0.067 mmol) of the crude aldehyde intermediate was suspended in 0.4 mL of t-BuOH and treated with 260 μL of 5% NaH_2PO_4 in water and 780 μL of 0.5 N KMnO_4 solution. After 1 hour the reaction mixture was concentrated in vacuo and the residue was partitioned between 30 mL water and 60 mL of EtAOc. The aqueous phase was extracted with EtAOc (2x10 mL) and the combined organic phases were washed with brine (1x10 mL) and dried over MgSO_4 . No 15 product could be detected in this organic phase. The aqueous phase was acidified to pH 1.0 with conc HCl and extracted with EtAOc (3x50 mL). The combined organic phases were washed with water (2x15 mL) and brine (1x15 mL) and dried over MgSO_4 . The solution was dried over MgSO_4 , filtered and concentrated in vacuo to give 20 mg of a white solid, 59% yield. $^1\text{H-NMR}$ (CD_3OD): 0.82 (t, 3H, $J = 7.3\text{Hz}$), 1.31 (m, 2H), 1.68 (m, 2H), 2.74 (3 line m, $J = 8.03$), 5.38 (bs, 2H), 7.08 (m, 4H), 7.48 (m, 2H), 7.58 (m, 2H), 7.62 (d, 1H, $J = 8.4\text{Hz}$), 8.28 (dd, 1H, $J = 1.9, 8.7\text{Hz}$), 8.80 (d, 1H, $J = 1.9\text{Hz}$). FABMS m/e: 481 ($M^+ + 1$) calc. for 20 $\text{C}_{27}\text{H}_{24}\text{N}_6\text{O}_3$

EXAMPLE 89

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2-Butyl-5-carboxy-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one

30 To 50 mg (0.11 mmol) of the product of Example 87 suspended in 3 mL of CH_2Cl_2 was added 500 mg of activated MnO_2 and a spatula tip full of activated 3A° molecular sieves. The mixture was vigorously stirred overnight under N_2 . Earlier experiments had indicated that the resulting aldehyde was very insoluble and had a propensity to adhere to the MnO_2 . Consequently, the reaction mixture was concentrated in vacuo and the crude mixture treated with 0.6 mL of t-BuOH, 0.42 mL of 5% aqueous NaH_2PO_4 and 1.25 mL of 0.5 N KMnO_4 . The solvent was removed in vacuo and the residue suspended in a mixture of 40 mL of EtAOc and 40 mL of water. The mixture was then filtered to remove the MnO_2 and the solid residue was washed with water and EtAOc. The resulting emulsion was treated with 5 mL of 1N NaOH to make the aqueous phase basic and break up the emulsion. The aqueous phase was extracted with EtAOc (3x50 mL) and then acidified with 1N HCl. The aqueous phase was extracted with EtAOc (3x50 mL) and the combined organic 35 extracts of the acidified solution were washed with brine (1x50 mL) and dried over MgSO_4 . The mixture was filtered and concentrated in vacuo to give 35.5 mg (0.07 mmol) of a solid, 69 % yield. $^1\text{H-NMR}$ (CD_3OD 300MHz): 0.91 (t, 3H, $J = 7.38\text{ Hz}$), 1.39 (m, 2H), 1.72 (m, 2H), 2.77 (7.9 Hz), 5.44 (bs, 2H), 7.14 (AB, 4H, $J = 9.2\text{ Hz}$), 7.47-7.79 (m, 6H), 7.82 (t, 1H, $J = 7.1\text{ Hz}$). FABMS m/e: 481 ($M^+ + 1$) calc. for $\text{C}_{27}\text{H}_{24}\text{N}_6\text{O}_3$

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EXAMPLE 9050 2-Butyl-6-carbomethoxy-3-[(2'-(tetrazol-5-yl)biphen-4-yl)-methyl]quinazolin-4(3H)-one

To a suspension of 65 mg (0.14 mmol) of the product from Example 86 in 3 mL of CH_2Cl_2 was added 650 mg of MnO_2 and 200 mg of powdered activated 3A° molecular sieves. The reaction mixture was stirred for 3 hours at which time TLC (70:30:1, EtAOc: hexane: acetic acid) indicated complete conversion to 55 the less polar aldehyde intermediate. The reaction mixture was concentrated in vacuo and the residue was suspended in 3 mL of MeOH. To this suspension was added 35 mg (0.7 mmol) of NaCN and 12 mg (0.21 mmol) of acetic acid. The reaction mixture was stirred over night and then filtered through celite. The solid residue was washed with 20 mL of MeOH. The filtrate was concentrated in vacuo and the residue was

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redisolved in 65 mL of EtAOc. The solution was washed with water (3x40 mL), brine (1x40 mL) and dried over MgSO₄. The mixture was filtered and concentrated *in vacuo* to give 29 mg of an oil. The product was purified by flash chromatography over silica gel eluting with 50:49:1 EtAOc:hexane:acetic acid to give 19 mg (0.04 mmol) of a white foam, 27% yield. ¹H-NMR (CDCl₃ 300MHz): 0.93 (t, 3H, J = 7.38 Hz), 1.43 (m, 2H), 1.79 (m, 2H), 2.78 (3 line m, 2H, J = 8.08Hz), 3.95 (s, 3H), 5.38 bs, 2H), 7.16 (s, 4H), 7.40 (d, 1H, 1.6Hz), 7.53 (m, 2H), 7.67 (d, 1H, J = 8.5Hz), 8.04 (dd, 1H, J = 7.43, 1.6Hz), 8.34 (dd, 1H, J = 8.6, 2.0 Hz), 8.89 (d, 1H, J = 1.9Hz). FABMS m/e: 495 (M⁺ + 1) calc. for C₂₈H₂₆N₆O₃

10

EXAMPLE 91

2-Butyl-5-carbomethoxy-3-[(2'-*(*tetrazol-5-*y*l)biphen-4-*y*l)-methyl]quinazolin-4(3*H*)-one

15

The product of Example 87 was treated as described in Example 90 to give the crude ester. The product was purified by MPLC over a silica gel Lobar A column eluting with 60:40:1 EtAOc:hexane:acetic acid to give a white foam, 38% yield. ¹H-NMR (CDCl₃ 300MHz): 0.94 (t, 3H, J = 7.37Hz), 1.43 (m, 2H), 1.80 (m, 2H), 2.80 (3 line m, 2H, J = 8.2Hz), 3.96 (s, 3H), 5.34 (bs, 2H), 7.15 9s, 4H) < 7.39 (m, 2H), 7.54 (m, 2H), 7.77 (m, 2H), 8.07 (d, 1H). FABMS m/e: 495 (M⁺ + 1) calc. for C₂₈H₂₆N₆O₃

25

EXAMPLE 92

2-Butyl-6-(N-methyl)amino-3-[(2'-*(*tetrazol-5-*y*l)biphen-4-*y*l)methyl]quinazolin-4(3*H*)-one

30

A solution of 0.23 g (0.27 mmol) of the product from Example 46 in 50 mL of MeOH was hydrogenated at atmospheric pressure in the presence of 50 mg of 10% Pd/C. When the starting material had been consumed the reaction mixture was filtered through celite and the filtrate was concentrated *in vacuo* to give 0.19 g of a yellow foam. The product was purified by flash chromatography over silica gel eluting with 40% EtAOc/hexanes to give 71 mg (0.1 mmol) of 2-butyl-6-(N-methyl)amino-3-[(2'-*(*N-triphenylmethyl)-tetrazol-5-*y*l)biphen-4-*y*l)methyl]quinazolin-4(3*H*)-one. The column was further eluted with 70:30:1 EtAOc:hexane:acetic acid to give 43 mg of crude deprotected compound. The silica gel from the chromatography was washed with more 70:30:1 EtAOc:hexane:acetic acid to give after filtration a further small amount of the product. The combined deprotected products were repurified by flash chromatography over silica gel eluting with 70:30:1 EtAOc:hexane:acetic acid to give 39 mg (0.08 mmol) of 2-n-butyl-3-[(2'-*(*tetrazol-5-*y*l)biphen-4-*y*l)methyl]-6-(N-methyl)aminoquinazolin-4(3*H*)-one. 66% overall yield. The deprotected material may be deprotected as in Example 54 to give an additional quantity of the desired product. ¹H-NMR (CDCl₃ 300MHz): 0.89 (t, 3H, J = 7.4Hz), 1.39 (m, 2H), 1.71 (m, 2H), 2.65 (3 line m, 2H, J = 8.3Hz), 2.89 (s, 3H), 5.33 (bs, 2H), 7.02 (dd, 1H, J = 2.8, 8.8Hz), 7.08 (s, 4H), 7.19 (d, 1H, J = 2.7Hz), 7.39 (m, 2H), 7.52 (m, 2H), 8.01 (dd, 1H). FABMS m/e: 466 (M⁺ + 1) calc. for C₂₇H₂₇N₇O.

45

EXAMPLE 93

50

2-Butyl-6-(methylsulfonyl)-3-[(2'-*(*tetrazol-5-*y*l)biphen-4-*y*l)methyl]quinazolin-4(3*H*)-one

55

To a solution of 0.05 g (0.11 mmol) of the deprotected quinazolinone from Example 77 in 3 mL of acetic acid at room temperature was added 0.5 mL of 30% hydrogen peroxide. The reaction mixture was stirred over night and then concentrated *in vacuo*. The residue was purified by flash chromatography over silica gel eluting with 65:34:1 EtAOc:hexane:acetic acid. The product was dissolved in toluene and concentrated *in vacuo* to remove any acetic acid by azeotropic distillation to give 32 mg (0.06 mmol) of a white powder, 62% yield. ¹H-NMR (CDCl₃ 300MHz): 0.90 (t, 3H, J = 7.3Hz), 1.41 (m, 2H), 1.76 (m, 2H), 2.79 (3 line m, 2H, J = 8.03Hz), 3.10 (s, 3H), 5.34 (bs, 2H), 7.09 (s, 4H), 7.35-7.59 (m, 3H), 7.78 (d, 1H, J = 8.7Hz), 7.88 (dd, 1H,

J=1.5,7.6Hz), 8.18 (dd, 1H, J=2.2,8.6Hz), 8.75 (d, 1H, J=1.96Hz). FABMS m/e: 515(M⁺ + 1) calc. for C₂₇H₂₆N₆SO₃.

5

EXAMPLE 942-Butyl-6-(methylsulfinyl)-3-[(2'-tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one

10

To a solution of 43.7 mg (0.1 mmol) of the deprotected quinazolinone from Example 77 in 1 mL of acetic acid was added 12.4 mg (0.11 mmol) of a 30% H₂O₂ solution in water. After stirring overnight TLC (50:30:19:1 EtAOc:hexane:MeOH:acetic acid) indicated that the reaction was incomplete. Addition of a further 12.4 mg of the H₂O₂ solution gave, after 2 hours, complete conversion to a more polar product. The reaction mixture was concentrated *in vacuo* and residue was purified by flash chromatography over silica gel eluting with 50:30:19:1 EtAOc:hexane:MeOH:acetic acid to give 27 mg (0.05 mmol) of a white solid, 50% yield. ¹H-NMR (CDCl₃ 300MHz): 0.94 (t, 3H, J=7.3Hz), 1.42 (m, 2H), 1.81 (m, 2H), 2.71 (s, 3H), 2.76 (3 line m, 2H, J=6.0Hz), 5.31 and 5.57 (AB, 2H, J=16.2Hz), 7.18 (m, 4H), 7.39-7.61 (m, 3H), 7.83 (d, 1H, J=8.7Hz), 7.96 (d, 1H, J=7.6Hz), 8.06 (d, 1H, J=8.7Hz), 8.62 (d, 1H, J=1.8Hz). FABMS m/e: 499 (M⁺ + 1) calc. for C₂₇H₂₆N₆SO

25

EXAMPLE 952-Butyl-6-(N-methyl-N-isobutyloxycarbonyl)amino-3-[(2'-(N-triphenylmethyltetrazol-5-yl)-biphen-4-yl)methyl]quinazolin-4(3H)-one

30

The intermediate product of Example 92, 2-n-butyl-6-(N-methyl-amino)-3-[(2'-(N-triphenylmethyltetrazol-5-yl)-biphen-4-yl)methyl]quinazolin-4(3H)-one was converted to the title compound in the following manner. To a solution of 0.08 g (0.11 mmol) of the methyl amine in 1 ml of dry DMF was added 24.8 mg (0.244 mmol) of triethyl amine followed by 33 mg (0.24 mmol) of isobutylchloroformate. The reaction mixture was stirred over 48 hours and diluted with 25 ml of EtAOc. The solution was washed with water (2x10 ml), brine (1x10 mL) and dried over MgSO₄. The solution was filtered and concentrated *in vacuo* and the residue was purified by MPLC over silica gel eluting with 40% EtAOc/hexanes to give 0.052 g of a colorless oil, 55% yield. ¹H-NMR (CDCl₃-200MHz): 0.87-0.93 (m, 9H), 1.68 (m, 2H), 1.71 (m, 2H), 1.92 (m, 1H), 2.67 (3 line m, 2H, J=7.6Hz), 3.40 (s, 3H), 3.93 (d, 2H, J=6.6Hz), 5.31 (bs, 2H), 6.88-6.99 (m, 8H), 7.11 (d, 2H, J=6.6Hz), 7.22-7.36 (m, 10H), 7.45 (m, 2H), 7.68 (d, 1H, 7.7Hz), 7.75 (m, 1H), 7.94 (dd, 1H, J=6.3, 2.3 Hz), 8.12 (d, 1H, J=2.5Hz).

EXAMPLE 96

45

2-Butyl-3-[(2'-(N-benzenesulfonyl)carboxamidobiphen-4-yl)-methyl]-6-isopropylquinazolin-4(3H)-one

The carboxylic acid (0.05 g, 0.088 mMol), obtained from Example 62B was dissolved in dry THF (1 ml), and to the solution was added 1,1-carbonyl-diimidazole (0.030 g, 0.18 mMol). The mixture was refluxed for 4 hours and then cooled down to room temperature. To the reaction were then added benzenesulfonamide (0.031 g, 0.19 mMol) and DBU (0.029 g), and the mixture was refluxed for 7 hours. The reaction was then concentrated *in vacuo*, and the residue was treated with 5% aqueous citric acid (5 ml) and extracted with ethyl acetate (3 X 15 ml). The combined organic layer was washed with brine and then dried over anhydrous sodium sulfate. The crude product, obtained after removal of the solvent, was purified by flash-chromatography over silica-gel using 2% methanol in methylene chloride to give the titled compound. Yield 0.015 g (25%, amorphous solid). ¹H-NMR(CD₃OD): 0.92 (t, 3H, J=7.35Hz), 1.35 (d, 6H, J=6.9Hz), 1.40 (m, 2H), 1.71 (m, 2H), 2.76 (t, 2H, J=7.7Hz), 3.16 (m, 1H), 5.46 (broad s, 2H), 6.86-7.88 (m, 15H), 8.20 (d, 1H,

$J = 1.9$ Hz). FAB-MS: m/e 594 (M + H), 616 (M + Na).

PREPARATION OF 1,2 DISUBSTITUTED QUINAZOLIN-4(1H)-ONES

5

EXAMPLE 97

10

N-Valeroyl-2-aminobenzonitrile

15 To a solution of 500 mg 2-aminobenzonitrile (4.23 mmol), 514 mg triethylamine (5.08 mmol), and 50 mg DMAP (0.41 mmol) in 6 mL CH_2Cl_2 at 0 °C was added 562 mg valeryl chloride (4.66 mmol) dropwise over 1 minute. The mixture was warmed to room temperature and stirred for 20 minutes. The mixture was then diluted with water and brine and was extracted three times with ether. The combined organic material was dried over MgSO_4 , stripped of solvent in vacuo, and was purified by flash chromatography over silica eluting with 20% ethyl acetate in hexane to give the title compound. R_f 0.22 in 20% ethyl acetate in hexane.

20 $^1\text{H-NMR}$ (300 MHz, CDCl_3): 8.42 (d, 1H), 7.60-7.10 (m, 2H), 6.72 (m, 1H), 4.40 (br s, 1H), 2.46 (t, 2H), 1.74 (m, 2H), 1.43 (m, 2H), 0.97 (t, 3H)

EXAMPLE 98

25

N-Valeroyl-N-[(2'-t-butoxycarbonyl)biphen-4-yl]-methyl]-2-aminobenzonitrile

30 To a solution of 146 mg of the product from Example 97 (0.72 mmol), 250 mg (0.72 mmol) 4-bromomethyl-2'-t-butoxycarbonylbiphenyl, and 119 mg NaI (0.79 mmol) in 4 mL DMF was added 46 mg 60% NaH dispersion in oil (1.15 mmol) at room temperature. After 45 minutes the mixture was diluted with water and brine and then was extracted three times with ether. The combined organic material was dried over MgSO_4 , stripped off solvent in vacuo, and was purified by MPLC over silica eluting with 20% ethyl acetate in hexane. R_f 0.20 in 20% ethyl acetate in hexane. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 7.75 (d, $J = 7.7$ Hz, 2H), 7.58-7.20 (m, 9H), 6.99 (d, $J = 7.7$ Hz, 1H), 5.60 (d, $J = 14.5$ Hz, 1H), 4.42 (d, $J = 14.3$ Hz, 1H), 2.05 (m, 2H), 1.62 (m, 2H), 1.26 (s, 9H), 1.25 (m, 2H), 0.85 (t, 3H)

40

EXAMPLE 99

2-Butyl-1-[(2'-carboxy)biphen-4-yl]methyl]quinazolin-4(1H)-one

45

To a solution of the purified N-Valeroyl-N-[(2'-t-butoxycarbonyl)biphen-4-yl]-methyl]-2-aminobenzonitrile (from Example 98) in 4 mL methanol were added 245 mL 30% H_2O_2 and 720 mL 3.0 N NaOH at room temperature. The mixture was heated to reflux for 1 hour. An additional 245 mL 30% H_2O_2 was added and the mixture was refluxed for an additional 45 minutes. The solution was diluted with brine then extracted three times with ether. The combined organic material was dried over MgSO_4 , stripped of solvent in vacuo, and was flash chromatographed over silica eluting with 25% ethyl acetate in methylene chloride to give a white solid. R_f 0.13 in 25% ethyl acetate in methylene chloride. The solid was stirred in 4 mL CH_2Cl_2 and 4 mL TFA over 4 hours. The volatiles were removed in vacuo and the crude material was flash chromatographed over silica eluting with 1:4:95 acetic acid/methanol/ methylene chloride to give a white crystalline solid. R_f 0.14 in 1:4:95 acetic acid/methanol/ methylene chloride. $^1\text{H-NMR}$ (300 MHz, CD_3OD): δ 8.34 (m, 1H), 7.89-7.06 (m, 11H), 5.79 (s, 2H), 3.01 (3 line m, 2H), 1.81 (m, 2H), 1.45 (m, 2H), 0.95 (t, 3H). FABMS m/z 413 (M⁺ + 1).

In a similar fashion the following 1,2-dialkylated quinazolin-4(1H)-ones may be prepared:

2-Butyl-1-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(1H)-one;
 2-Propyl-1-[(2'-(tetrazol-5-yl)biphen-4-yl)-methyl]quinazolin-4(1H)-one;
 2-Butyl-6-methyl-1-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(1H)-one;
 6-Methyl-2-pentyl-1-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(1H)-one;
 5 2-Butyl-6-methyl-1-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(1H)-one;
 2-Butyl-5-methyl-1-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(1H)-one;
 2-Butyl-7-methyl-1-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(1H)-one;
 2-Butyl-6-nitro-1-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(1H)-one;
 2-Butyl-8-methyl-1-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(1H)-one;
 10 5-Benzyl-2-butyl-1-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(1H)-one.

EXAMPLE 100

15

Typical Pharmaceutical Compositions Containing a Compound of the Invention20 A: Dry Filled Capsules Containing 50 mg of Active Ingredient Per Capsule

Ingredient	Amount per capsule (mg)
2-Butyl-6-isopropyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one	50
Lactose	149
Magnesium stearate	1
Capsule (size No. 1)	200

30

The 2-butyl-6-isopropyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one can be reduced to a No. 60 powder and the lactose and magnesium stearate can then be passed through a No. 60 blotting cloth onto the powder. The combined ingredients can then be mixed for about 10 minutes and filled into a No. 1 dry gelatin capsule.

B: Tablet

40 A typical tablet would contain 2-butyl-6-isopropyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one (25 mg), pregelatinized starch USP (82 mg), microcrystalline cellulose (82 mg) and magnesium stearate (1 mg).

45 C: Combination Tablet

A typical combination tablet would contain, for example, a diuretic such as hydrochlorothiazide and consist of 2-butyl-6-isopropyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one (50 mg) pregelatinized starch USP (82 mg), microcrystalline cellulose (82 mg) and magnesium stearate (1 mg).

50

D: Suppository

55 Typical suppository formulations for rectal administration can contain 2-butyl-6-isopropyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]quinazolin-4(3H)-one (0.08-1.0 mg), disodium calcium edetate (0.25-0.5 mg), and polyethylene glycol (775-1600 mg). Other suppository formulations can be made by substituting, for example, butylated hydroxytoluene (0.04-0.08 mg) for the disodium calcium edetate and a hydrogenated vegetable oil (675-1400 mg) such as Suppocire L, Wecobee FS, Wecobee M, Witepsols, and the like, for

the polyethylene glycol. Further, these suppository formulations can also include another active ingredient such as another antihypertensive and/or a diuretic and/or an angiotensin converting enzyme and/or a calcium channel blocker in pharmaceutically effective amounts as described, for example, in C above.

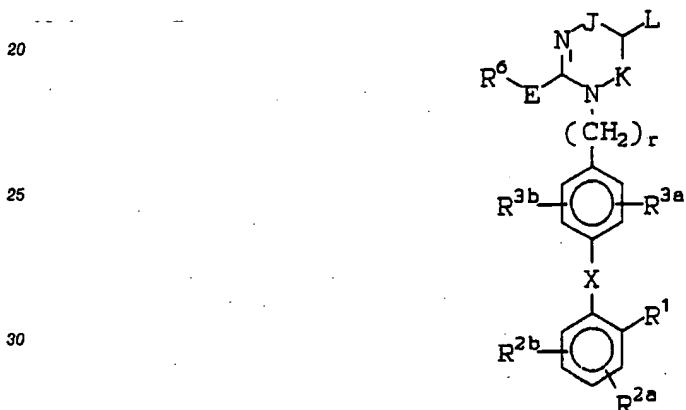
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E: Injection

A typical injectable formulation would contain 2-butyl-6-isopropyl-3-[(2'-(tetrazol-5-yl)biphen-4-yl)methyl]-10 quinazolin-4(3H)-one sodium phosphate dibasic anhydrous (11.4 mg) benzyl alcohol (0.01 ml) and water for injection (1.0 ml). Such an injectable formulation can also include a pharmaceutically effective amount of another active ingredient such as another antihypertensive and/or a diuretic and/or an angiotensin converting enzyme inhibitor and/or a calcium channel blocker.

15 **Claims**

1. A compound of formula (I):



wherein:

L is connected with J or K to form an aromatic ring as defined below;
 40 J is -C(=M)- or J and L are connected together to form a 6 carbon aromatic ring substituted with R^{7a}, R^{7b}, R^{8a} and R^{8b}, provided that only one of J and K is -C(=M)-; K is -C(=M)- or K and L are connected together to form a 6 carbon aromatic ring substituted with R^{7a}, R^{7b}, R^{8a} and R^{8b}, provided that only one of J and K is -C(=M)-;
 M is O or NR²²
 45 R¹ is
 (a) -CO₂R⁴,
 (b) -SO₃R⁵,
 (c) -NHSO₂CF₃,
 (d) -PO(OR⁵)₂,
 (e) -SO₂-NH-R⁹,
 50 (f) -CONHOR⁵,

OH O

(g) $-\text{C}(\text{OH})(\text{O})\text{R}^5,$
 $\text{R}^9 \text{O}\text{R}^5$

5

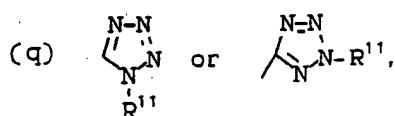
O

(h) $-\text{P}(\text{O})\text{R}^9$
 OR^5

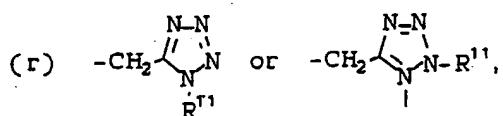
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- (i) $-\text{SO}_2\text{NH}$ -heteroaryl as defined below,
- (j) $-\text{CH}_2\text{SO}_2\text{NH}$ -heteroaryl as defined below,
- (k) $-\text{SO}_2\text{NH-CO-R}^{23},$
- (l) $-\text{CH}_2\text{SO}_2\text{NH-CO-R}^{23},$
- 15 (m) $-\text{CONH-SO}_2\text{R}^{23},$
- (n) $-\text{CH}_2\text{CONH-SO}_2\text{R}^{23},$
- (o) $-\text{NHSO}_2\text{NHCO-R}^{23},$
- (p) $-\text{NHCONHSO}_2\text{R}^{23},$

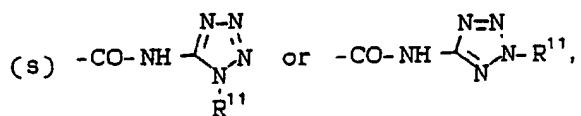
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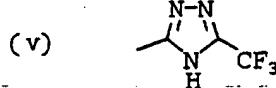
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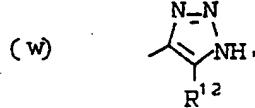
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- (t) $-\text{CONHNHSO}_2\text{CF}_3,$
- (u) $-\text{SO}_2\text{NH-CN},$

40



45



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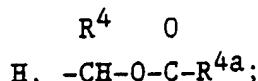
- (x) $-\text{PO}(\text{O}\text{R}^5)(\text{OR}^4),$
- (y) $-\text{SO}_2\text{NHCONR}^4\text{R}^{23};$

wherein heteroaryl is an unsubstituted, monosubstituted or disubstituted five or six membered aromatic ring which can optionally contain from 1 to 3 heteroatoms selected from the group consisting of O, N or S and wherein the substituents are members selected from the group consisting of -OH, -SH, $-\text{C}_1\text{-C}_4$ -alkyl, $-\text{C}_1\text{-C}_4$ -alkoxy, $-\text{CF}_3$, halo (Cl, Br, F, I), $-\text{NO}_2$, $-\text{CO}_2\text{H}$, $-\text{CO}_2-(\text{C}_1\text{-C}_4\text{-alkyl})$, $-\text{NH}_2$, $-\text{NH}(\text{C}_1\text{-C}_4\text{-alkyl})$ and $-\text{N}(\text{C}_1\text{-C}_4\text{-alkyl})_2$;

R^{2a} and R^{2b} are each independently

- (a) H,
- (b) halogen, (Cl, Br, I, F)

- (c) NO_2 ,
- (d) NH_2 ,
- (e) $\text{C}_1\text{-C}_4\text{-alkylamino}$,
- (f) $\text{di}(\text{C}_1\text{-C}_4\text{-alkyl})\text{amino}$
- 5 (g) SO_2NHR^9 ,
- (h) CF_3 ,
- (i) $\text{C}_1\text{-C}_6\text{-alkyl}$,
- (j) $\text{C}_1\text{-C}_6\text{-alkoxy}$,
- (k) $\text{C}_1\text{-C}_6\text{-alkyl-S-}$,
- 10 (l) $\text{C}_2\text{-C}_6\text{-alkenyl}$,
- (m) $\text{C}_2\text{-C}_6\text{-alkynyl}$,
- (n) aryl as defined below,
- (o) aryl($\text{C}_1\text{-C}_4\text{-alkyl}$),
- (p) $\text{C}_3\text{-C}_7\text{-cycloalkyl}$;
- 15 R^{3a} is
 - (a) H,
 - (b) halo (Cl, Br, I, F)
 - (c) $\text{C}_1\text{-C}_6\text{-alkyl}$,
 - (d) $\text{C}_1\text{-C}_6\text{-alkoxy}$,
 - (e) $\text{C}_1\text{-C}_6\text{-alkoxyalkyl}$;
- 20 R^{3b} is
 - (a) H,
 - (b) halo (Cl, Br, I, F)
 - (c) NO_2 ,
 - (d) $\text{C}_1\text{-C}_6\text{-alkyl}$,
 - (e) $\text{C}_1\text{-C}_6\text{-acyloxy}$,
 - (f) $\text{C}_3\text{-C}_7\text{-cycloalkyl}$,
 - (g) $\text{C}_1\text{-C}_6\text{-alkoxy}$,
 - (h) $-\text{NHSO}_2\text{R}^4$,
 - (i) hydroxy-($\text{C}_1\text{-C}_4\text{-alkyl}$),
 - (j) aryl-($\text{C}_1\text{-C}_4\text{-alkyl}$),
 - (k) $\text{C}_1\text{-C}_4\text{-alkylthio}$,
 - (l) $\text{C}_1\text{-C}_4\text{-alkyl sulfinyl}$,
 - (m) $\text{C}_1\text{-C}_4\text{-alkyl sulfonyl}$,
 - (n) NH_2 ,
 - (o) $\text{C}_1\text{-C}_4\text{-alkylamino}$,
 - (p) $\text{di}(\text{C}_1\text{-C}_4\text{-alkyl})\text{amino-}$,
 - (q) fluoro- $\text{C}_1\text{-C}_4\text{-alkyl}$,
 - (r) $-\text{SO}_2\text{NHR}^9$,
 - (s) aryl as defined below,
 - (t) furyl,
 - (u) CF_3 ,
 - (v) $\text{C}_2\text{-C}_6\text{-alkenyl}$,
 - (w) $\text{C}_2\text{-C}_6\text{-alkynyl}$;
- 25 45 wherein aryl is phenyl or naphthyl optionally substituted with one or two substituents selected from the group consisting of halo(Cl, Br, I, F), $\text{N}(\text{R}^4)_2$, CO_2R^4 , $\text{C}_1\text{-C}_4\text{-alkyl}$, $\text{C}_1\text{-C}_4\text{-alkoxy}$, NO_2 , CF_3 , $\text{C}_1\text{-C}_4\text{-alkylthio}$, or OH;
- 40 R^4 is H, aryl as defined above or straight chain or branched $\text{C}_1\text{-C}_6\text{-alkyl}$, optionally substituted with aryl as defined above;
- 50 R^{4a} is aryl as defined above or straight chain or branched $\text{C}_1\text{-C}_6\text{-alkyl}$ optionally substituted with aryl as defined above;
- R^5 is



E is a single bond, $-\text{NR}^{13}(\text{CH}_2)_s-$, $-\text{S}(\text{O})_x(\text{CH}_2)_s-$ where x is 0 to 2 and s is 0 to 5, $-\text{CH}(\text{OH})-$, $-\text{O}-$, $\text{CO}-$; R^6 is

(a) aryl as defined above optionally substituted with 1 or 2 substituents selected from the group consisting of halo (Cl, Br, I, F) $-\text{O}-\text{C}_1\text{-C}_4\text{-alkyl}$, $\text{C}_1\text{-C}_4\text{-alkyl}$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{SO}_2\text{NR}^9\text{R}^{10}$, $-\text{S}-\text{C}_1\text{-C}_4\text{-alkyl}$, $-\text{OH}$, $-\text{NH}_2$, $\text{C}_3\text{-C}_7\text{-cycloalkyl}$, $\text{C}_3\text{-C}_{10}\text{-alkenyl}$;

5 (b) straight chain or branched $\text{C}_1\text{-C}_6\text{-alkyl}$, $\text{C}_2\text{-C}_5\text{-alkenyl}$ or $\text{C}_2\text{-C}_5\text{-alkynyl}$ each of which can be optionally substituted with a substituent selected from the group consisting of aryl as defined above, $\text{C}_3\text{-C}_7\text{-cycloalkyl}$, halo (Cl, Br, I, F) $-\text{OR}^4$, CF_3 , CF_2CF_3 , $-\text{NH}_2$, $-\text{NH}(\text{C}_1\text{-C}_4\text{-alkyl})$, $-\text{N}(\text{C}_1\text{-C}_4\text{-alkyl})_2$, $-\text{NH}-\text{SO}_2\text{R}^4$, $-\text{COOR}^4$, $-\text{SO}_2\text{NHR}^8$; or

10 (c) an unsubstituted, monosubstituted or disubstituted heteroaromatic 5 or 6 membered cyclic ring which can contain one or two members selected from the group consisting of N, O, S, and wherein the substituents are members selected from the group consisting of $-\text{OH}$, $-\text{SH}$, $\text{C}_1\text{-C}_4\text{-alkyl}$, $\text{C}_1\text{-C}_4\text{-alkyloxy}$ $-\text{CF}_3$, halo (Cl, Br, I, F), or $-\text{NO}_2$;

(d) $\text{C}_3\text{-C}_7\text{-cycloalkyl}$;

15 (e) perfluoro- $\text{C}_1\text{-C}_4\text{-alkyl}$;

(f) H;

R^{7a} and R^{7b} are independently

(a) H,

(b) straight chain or branched $\text{C}_1\text{-C}_6\text{-alkyl}$, $\text{C}_2\text{-C}_5\text{-alkenyl}$ or $\text{C}_2\text{-C}_5\text{-alkynyl}$,

20 (c) halo(Cl, Br, I, F)

(d) CF_3 , or

(e) when R^{7a} and R^{7b} are bonded to adjacent carbon atoms, they can be joined to form a phenyl ring;

R^{8a} and R^{8b} are independently

(a) H,

25 (b) $\text{C}_1\text{-C}_6\text{-alkyl}$ optionally substituted with a substituent selected from the group consisting of $-\text{OH}$, $-\text{guanidino}$, $\text{C}_1\text{-C}_4\text{-alkoxy}$, $-\text{N}(\text{R}^4)_2$, COOR^4 , $-\text{CON}(\text{R}^4)_2$, $-\text{O}-\text{COR}^4$, $-\text{aryl}$, $-\text{heteroaryl}$, $-\text{S}(\text{O})_x\text{R}^{23}$, $-\text{tetrazol-5-yl}$, $-\text{CONHSO}_2\text{R}^{23}$, $-\text{SO}_2\text{NH-heteroaryl}$, $-\text{SO}_2\text{NHCOR}^{23}$, $-\text{PO}(\text{OR}^4)_2$, $-\text{PO}(\text{OR}^4)\text{R}^9$, $-\text{SO}_2\text{NH-CN}$, $-\text{NR}^{10}\text{COOR}^{23}$,

(c) $-\text{CO-aryl}$,

(d) $\text{C}_3\text{-C}_7\text{-cycloalkyl}$,

30 (e) -halo (Cl, Br, I, F),

(f) $-\text{OH}$,

(g) $-\text{OR}^{23}$,

(h) $-\text{C}_1\text{-C}_4\text{-perfluoroalkyl}$,

(i) $-\text{S}(\text{O})_x\text{R}^{23}$,

35 (j) $-\text{COOR}^4$,

(k) $-\text{SO}_3\text{H}$,

(l) $-\text{NR}^4\text{R}^{23}$,

(m) $-\text{NR}^4\text{COR}^{23}$,

(n) $-\text{NR}^4\text{-COOR}^{23}$,

40 (o) $-\text{SO}_2\text{NR}^9\text{R}^{10}$,

(p) $-\text{NO}_2$,

(q) $-\text{N}(\text{R}^4)\text{SO}_2\text{R}^{23}$,

(r) $-\text{NR}^4\text{CONR}^4\text{R}^{23}$,

45 (s)

0
 $-\text{OCNR}^{23}\text{R}^9$,

50 (t) aryl or -heteroaryl as defined above.

(u) $-\text{NHSO}_2\text{CF}_3$,

(v) $-\text{SO}_2\text{NH-heteroaryl}$,

(w) $-\text{SO}_2\text{NHCOR}^{23}$,

55 (x) $-\text{CONHSO}_2\text{R}^{23}$,

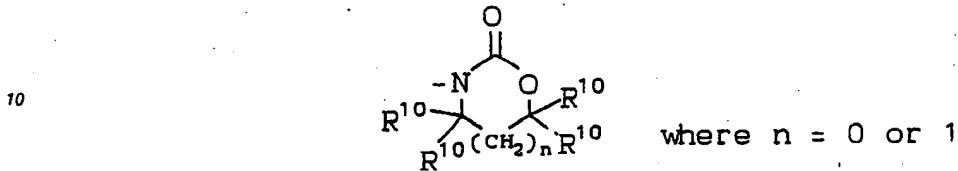
(y) $-\text{PO}(\text{OR}^4)_2$,

(z) $-\text{PO}(\text{OR}^4)_2$,

(aa) -tetrazol-5-yl,

(bb) -CONH(tetrazol-5-yl),
 (cc) -COR⁴,
 (dd) -SO₂NHCN,

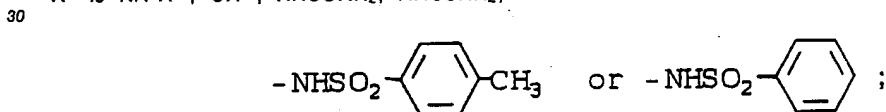
5 (ee)



15 R⁹ is H, C₁-C₅-alkyl, aryl, or arylmethyl;
 R¹⁰ is H, C₁-C₄-alkyl;
 R¹¹ is H, C₁-C₆-alkyl, C₁-C₄-alkenyl, C₁-C₄-alkoxy alkyl, or

20 -CH₂ ; R²⁰

R¹² is -CN, -NO₂ or -CO₂R⁴;
 25 R¹³ is H, (C₁-C₄-alkyl)CO-, C₁-C₆-alkyl, allyl, C₃-C₆-cycloalkyl, aryl or arylmethyl;
 R¹⁴ is H, C₁-C₈-alkyl, C₁-C₈-perfluoroalkyl, C₃-C₆-cycloalkyl, aryl or arylmethyl;
 R¹⁵ is H, C₁-C₆-alkyl;
 R¹⁶ is H, C₁-C₆-alkyl, C₃-C₆-cycloalkyl, aryl or arylmethyl;
 R¹⁷ is -NR⁹R¹⁰, -OR¹⁰, -NHCONH₂, -NHCSNH₂,



35 R¹⁸ and R¹⁹ are independently C₁-C₄-alkyl or taken together are -(CH₂)_q- where q is 2 or 3;
 R²⁰ is H, -NO₂, -NH₂, -OH or -OCH₃;
 R²¹ is H, aryl, or C₁-C₄-alkyl optionally substituted with aryl, -NH₂, -NH(C₁-C₄-alkyl), -N(C₁-C₄-alkyl)₂, -CO₂R⁴, -OH, -SO₃H, -SO₂NH₂;

40 R²² is
 (a) aryl as defined above,
 (b) heteroaryl as defined above,
 (c) C₁-C₄-alkyl optionally substituted with a substituent selected from the group consisting of aryl as defined above, heteroaryl as defined above, -OH, -NH₂, -NH(C₁-C₄-alkyl), -N(C₁-C₄-alkyl)₂, -CO₂R⁴, halo(Cl, Br, F, I), -CF₃;

45 R²³ is
 (a) aryl as defined above,
 (b) heteroaryl as defined above,
 (c) C₃-C₇-cycloalkyl,
 (d) C₁-C₆-alkyl optionally substituted with a substituent selected from the group consisting of aryl as defined above, heteroaryl as defined above, -OH, -SH, C₁-C₄-alkyl, -O(C₁-C₄-alkyl), -S(C₁-C₄-alkyl), CF₃, halo (Cl, Br, F, I), -NO₂, -CO₂H, CO₂-C₁-C₄-alkyl, -NH₂, -NH(C₁-C₄-alkyl), -N(C₁-C₄-alkyl)₂, -PO₃H₂, -PO(OH)(O-C₁-C₄-alkyl), -PO (OR⁴)R⁹,
 (e) perfluoro-C₁-C₄-alkyl;

55 X is
 (a) a carbon-carbon single bond,
 (b) -CO-,
 (c) -O-,

(d) -S-,

(e) -N-,
R¹³

5

(f) -CON-,
R¹⁵

10

(g) -NCO-,
R¹⁵

10

(h) -OCH₂-,(i) -CH₂O-15 (j) -SCH₂-,(k) -CH₂S-,(l) -NHC(R⁹)(R¹⁰),(m) -NR⁹SO₂-,(n) -SO₂NR⁹-,20 (o) -C(R⁹)(R¹⁰)NH-,

(p) -CH=CH-,

(q) -CF=CF-,

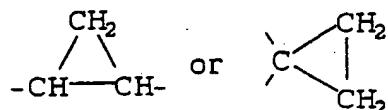
(r) -CH=CF-,

(s) -CF=CH-,

25 (t) -CH₂CH₂-,(u) -CF₂CF₂-,

(v)

30



or

35

(w) -CH-,
OR¹⁴

40

(x) -CH-,
OCOR¹⁶

45

(y) -C-,
NR¹⁷

50

(z) -C-
R¹⁸O / OR¹⁹

55

r is 1 or 2; and
the pharmaceutically acceptable salts thereof.

2. A compound of Claim 1 wherein:

J is $-\text{C}(\text{O})-$;

K and L are connected together to form a 6 carbon aromatic ring substituted with R^{7a} , R^{7b} , R^{8a} and R^{8b} ;

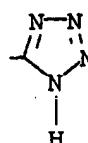
R^1 is

5 (a) $-\text{COOH}$,

(b)

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15



20

(c) $-\text{NH}-\text{SO}_2\text{CF}_3$;

(d) $-\text{SO}_2\text{NH}$ -heteroaryl as defined above,

(e) $-\text{CH}_2\text{SO}_2\text{NH}$ -heteroaryl as defined above,

25 (f) $-\text{SO}_2\text{NH}-\text{CO}-\text{R}^{23}$,

(g) $-\text{CH}_2\text{SO}_2\text{NH}-\text{CO}-\text{R}^{23}$,

(h) $-\text{CONH}-\text{SO}_2\text{R}^{23}$,

(i) $-\text{CH}_2\text{CONH}-\text{SO}_2\text{R}^{23}$,

(j) $-\text{NHSO}_2\text{NHCO}-\text{R}^{23}$,

30 (k) $-\text{NHCONHSO}_2-\text{R}^{23}$,

R^{2a} is H;

R^{2b} is H, F, Cl, CF_3 , $\text{C}_1\text{-C}_6$ -alkyl $\text{C}_2\text{-C}_4$ -alkenyl or $\text{C}_2\text{-C}_4$ -alkynyl;

R^{3a} is H;

R^{3b} is H, F, Cl, CF_3 , $\text{C}_1\text{-C}_4$ -alkyl, $\text{C}_2\text{-C}_4$ -alkenyl, $\text{C}_2\text{-C}_4$ -alkynyl, $\text{C}_5\text{-C}_6$ -cycloalkyl, $-\text{COOCH}_3$, $-\text{COOC}_2\text{H}_5$,

35 $-\text{SO}_2\text{-CH}_3$, NH_2 , $-\text{N}(\text{C}_1\text{-C}_4\text{-alkyl})_2$ or $-\text{NH}-\text{SO}_2\text{CH}_3$;

E is a single bond, $-\text{O}-$ or $-\text{S}-$;

R^6 is

(a) $\text{C}_1\text{-C}_5$ alkyl optionally substituted with a substituent selected from the group consisting of $\text{C}_3\text{-C}_5$ -cycloalkyl, Cl, CF_3 , $-\text{CCl}_3$, $-\text{O}-\text{CH}_3$, $-\text{OC}_2\text{H}_5$, $-\text{S}-\text{CH}_3$, $-\text{S}-\text{C}_2\text{H}_5$, phenyl, or F;

40 (b) $\text{C}_2\text{-C}_5$ -alkenyl or $\text{C}_2\text{-C}_5$ -alkynyl;

(c) $\text{C}_3\text{-C}_5$ -cycloalkyl;

R^{7a} and R^{7b} are each H;

R^{8a} and R^{8b} are independently

(a) H,

45 (b) $\text{C}_1\text{-C}_4$ -alkyl optionally substituted with COOR^4 , OCOR^{4a} , OH, aryl;

(c) $\text{C}_2\text{-C}_4$ -alkenyl,

(d) -OH,

(e) $-\text{NO}_2$,

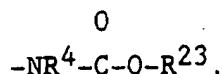
50

R^{40}

(f) $-\text{N}-\text{C}-\text{R}^{23}$,

55 (g) $-\text{C}_1\text{-C}_4$ alkoxy,

(h)



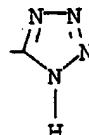
5 (i) $-\text{NR}^4\text{R}^{23}$,
 (j) halo(Cl, F, Br),
 (k) $-\text{CF}_3$,
 (l) $-\text{CO}_2\text{R}^4$,
 (m) $-\text{CO-aryl}$ as defined above,
 10 (n) $-\text{S(O)}_x\text{C}_1\text{-C}_4\text{-alkyl}$,
 (o) $-\text{SO}_2\text{-NH-C}_1\text{-C}_4\text{-alkyl}$,
 (p) $-\text{SO}_2\text{-NH-aryl}$ as defined above,



20 (r) aryl as defined above,
 (s) $-\text{NR}^4\text{CONR}^4\text{R}^{23}$;
 X is a C-C single bond;
 r is one.
 3. A compound of Claim 1 wherein:
 K is $-\text{C}(\text{O})-$;
 25 J and L are connected together to form a 6 carbon aromatic ring substituted with R^{7a} , R^{7b} , R^{8a} and R^{8b} ;
 R^1 is (a) $-\text{COOH}$,

(b)

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(c) $-\text{NH-SO}_2\text{CF}_3$;
 (d) $-\text{SO}_2\text{NH-heteroaryl}$ as defined above,
 40 (e) $-\text{CH}_2\text{SO}_2\text{NH-heteroaryl}$ as defined above,
 (f) $-\text{SO}_2\text{NH-CO-R}^{23}$,
 (g) $-\text{CH}_2\text{SO}_2\text{NH-CO-R}^{23}$,
 (h) $-\text{CONH-SO}_2\text{R}^{23}$,
 (i) $-\text{CH}_2\text{CONH-SO}_2\text{R}^{23}$,
 45 (j) $-\text{NHSO}_2\text{NHCO-R}^{23}$,
 (k) $-\text{NHCONHSO}_2\text{-R}^{23}$,
 R^{2a} is H;
 R^{2b} is H, F, Cl, CF_3 , $\text{C}_1\text{-C}_4\text{-alkyl}$, $\text{C}_2\text{-C}_4\text{-alkenyl}$, $\text{C}_2\text{-C}_4\text{-alkynyl}$;
 R^{3a} is H;
 50 R^{3b} is H, F, Cl, CF_3 , $\text{C}_1\text{-C}_6\text{-alkyl}$, $\text{C}_2\text{-C}_4\text{-alkenyl}$, $\text{C}_2\text{-C}_4\text{-alkynyl}$ $\text{C}_5\text{-C}_6\text{-cycloalkyl}$, $-\text{COOCH}_3$, $-\text{COOC}_2\text{H}_5$,
 $-\text{SO}_2\text{-CH}_3$, NH_2 , $-\text{N}(\text{C}_1\text{-C}_4\text{-alkyl})_2$, or $-\text{NH-SO}_2\text{CH}_3$;
 E is a single bond, $-\text{O-}$ or $-\text{S-}$;
 R^6 is
 (a) $\text{C}_1\text{-C}_5$ alkyl optionally substituted with a substituent selected from the group consisting of methyl, ethyl,
 55 Cl, CF_3 , CCl_3 , $-\text{O-CH}_3$, $-\text{OC}_2\text{H}_5$, $-\text{S-CH}_3$, $-\text{S-C}_2\text{H}_5$, phenyl, or F;
 (b) $\text{C}_2\text{-C}_5\text{-alkenyl}$ or $\text{C}_2\text{-C}_5\text{-alkynyl}$;
 (c) $\text{C}_3\text{-C}_5\text{-cycloalkyl}$;
 R^{7a} and R^{7b} are each H;

R^{8a} and R^{8b} are independently

- (a) H,
- (b) C_1 - C_4 -alkyl optionally substituted with $COOR^4$, $OCOR^{4a}$, OH, aryl,
- (c) C_2 - C_4 -alkenyl,
- 5 (d) -OH,
- (e) $-NO_2$,

10 (f)
$$\begin{array}{c} R^4O \\ | \\ -N-C-R^{23}, \end{array}$$

(g) $-C_1$ - C_4 -alkoxy,

15 (h)

20 (i) $-NR^4R^{23}$,

(j) -halo(Cl, F, Br),

(k) $-CF_3$,

25 (l) $-CO_2R^4$,

(m) -CO-aryl as defined above,

(n) $-S(O)_x-C_1$ - C_4 -alkyl

(o) $-SO_2-NH-C_1$ - C_4 -alkyl,

(p) $-SO_2-NH$ -aryl as defined above,

30 (q)
$$\begin{array}{c} R^4 \\ | \\ -N-SO_2CH_3, \end{array}$$

35 (r) -aryl as defined above,

(s) $-NR^4-CO NR^4R^{23}$,

X is a C-C single bond or -CO-; and,

r is one.

4. A compound of Claim 1 wherein:

40 K is $-C(=NR^{22})-$;

J and L are connected together to form a 6 carbon aromatic ring substituted with R^{7a} , R^{7b} , R^{8a} and R^{8b} ;

R^1 is (a) COOH,

45

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55

(c) $-NH-SO_2CF_3$;

(d) $-\text{SO}_2\text{NH}$ -heteroaryl as defined above,
 (e) $-\text{CH}_2\text{SO}_2\text{NH}$ -heteroaryl as defined above,
 (f) $-\text{SO}_2\text{NH-CO-R}^{23}$,
 (g) $-\text{CH}_2\text{SO}_2\text{NH-CO-R}^{23}$,
 5 (h) $-\text{CONH-SO}_2\text{R}^{23}$,
 (i) $-\text{CH}_2\text{CONH-SO}_2\text{R}^{23}$,
 (j) $-\text{NHSO}_2\text{NHCO-R}^{23}$,
 (k) $-\text{NHCONHSO}_2\text{R}^{23}$,
 R^{23} is H;
 10 R^{23} is H, F, Cl, CF_3 or $\text{C}_1\text{-C}_6$ -alkyl, $\text{C}_2\text{-C}_4$ -alkenyl, $\text{C}_2\text{-C}_4$ -alkynyl;
 R^{33} is H;
 R^{33} is H, F, Cl, CF_3 , $\text{C}_1\text{-C}_4$ -alkyl, $\text{C}_2\text{-C}_4$ -alkenyl, $\text{C}_2\text{-C}_4$ -alkynyl;
 $\text{C}_5\text{-C}_6$ -cycloalkyl, $-\text{COOCH}_3$, $-\text{COOC}_2\text{H}_5$, $-\text{SO}_2\text{-CH}_3$, NH_2 , $-\text{N}(\text{C}_1\text{-C}_4\text{-alkyl})_2$, or $-\text{NH-SO}_2\text{CH}_3$;
 E is a single bond, $-\text{O-}$ or $-\text{S-}$;
 15 R^6 is
 (a) $\text{C}_1\text{-C}_5$ alkyl optionally substituted with a substituent selected from the group consisting of $\text{C}_3\text{-C}_5$ -cycloalkyl, Cl, CF_3 , CCl_3 , $-\text{O-CH}_3$, $-\text{OC}_2\text{H}_5$, $-\text{S-CH}_3$, $-\text{S-C}_2\text{H}_5$ or phenyl, or F;
 (b) $\text{C}_2\text{-C}_5$ -alkenyl or $\text{C}_2\text{-C}_5$ -alkynyl;
 (c) $\text{C}_3\text{-C}_5$ -cycloalkyl;
 20 R^{7a} and R^{7b} are each H or when R^{7a} and R^{7b} are bonded to adjacent carbon atoms, they can be joined to form a phenyl ring;
 R^{8a} and R^{8b} are independently
 (a) H,
 (b) $\text{C}_1\text{-C}_4$ -alkyl optionally substituted with COOR^4 , OCOR^{4a} , OH, aryl,
 25 (c) $\text{C}_2\text{-C}_4$ -alkenyl,
 (d) -OH,
 (e) $-\text{NO}_2$,

30 R^{40}
 (f) $-\text{N-C-R}^{23}$,

(g) $-\text{C}_1\text{-C}_4$ -alkoxy,

35 (h)

0
 $-\text{NR}^4-\text{C-OR}^{23}$,

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(i) $-\text{NR}^4\text{R}^{23}$,
 (j) halo(Cl, F, Br),
 (k) $-\text{CF}_3$,
 (l) $-\text{CO}_2\text{R}^4$,
 45 (m) $-\text{CO-aryl}$ as defined above,
 (n) $-\text{S(O)}_x\text{C}_1\text{-C}_4$ -alkyl
 (o) $-\text{SO}_2\text{NH-C}_1\text{-C}_4$ -alkyl,
 (p) $-\text{SO}_2\text{NH-aryl}$ as defined above,

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R^4
 (q) $-\text{N-SO}_2\text{CH}_3$,

55 (r) aryl as defined above,

(s) $-\text{NR}^4\text{CONR}^4\text{R}^{23}$,

X is a single bond;

r is one.

5. A pharmaceutical composition useful in the treatment of hypertension which comprises a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound of Claim 1.
6. The composition of Claim 5 which includes an antihypertensive or a diuretic or an angiotensin converting enzyme or a calcium channel blocker which are members selected from the group consisting of:
 - 5 amiloride, atenolol, bendroflumethiazide, chlorothalidone, chlorothiazide, clonidine, cryptenamine acetates and cryptenamide tannates, deserpidine, diazoxide, guanethidine sulfate, hydralazine hydrochloride, hydrochlorothiazide, metolazone, metoprolol tartate, methyclothiazide, methyldopa, methyldopate hydrochloride, minoxidil, pargyline hydrochloride, polythiazide, prazosin, propranolol, *rauwolfia serpentina*, rescinnamine, reserpine, sodium nitroprusside, spironolactone, timolol maleate, trichlormethiazide, trimethophan
 - 10 camsylate, benzthiazide, quinethazone, ticryfan, triamterene, acetazolamide, aminophylline, cyclothiazide, ethacrynic acid, furosemide, merethoxylline procaine, sodium ethacrynat, captopril, delapril hydrochloride, enalapril, enalaprilat, fosinopril sodium, lisinopril, pentopril, quinapril hydrochloride, ramapril, teprotide, zofenopril calcium, diflusinal, diltiazem, felodipine, nicardipine, nifedipine, niludipine, nimodipine, nisoldipine, nitrendipine, as well as admixtures and combinations thereof.
- 15 7. An ophthalmological formulation for the treatment of ocular hypertension comprising an ophthalmologically acceptable carrier and an effective ocular antihypertensive amount of a compound of Claim 1.

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European
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EUROPEAN SEARCH
REPORT

Application Number

EP 90 30 7126

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
A,D	EP-A-0 253 310 (E.I. DU PONT DE NEMOURS AND CO.) * claims 1,5 -----	1,5	C 07 D 239/91 C 07 D 239/88 C 07 D 239/95 C 07 D 239/96 C 07 D 403/10 C 07 D 239/94 C 07 D 401/14 C 07 D 403/12 A 61 K 31/505
A,D	EP-A-0 291 969 (E.I. DU PONT DE NEMOURS AND CO.) * claim 1 -----	1	
A	US-A-3 936 453 (G.E. HARDTMANN) * the whole document -----	1,5	
P,A	EP-A-0 323 841 (E.I. DU PONT DE NEMOURS AND CO.) * claims 1,10-12 -----	1,5	
TECHNICAL FIELDS SEARCHED (Int. Cl.5)			
C 07 D 239/00 C 07 D 403/00 C 07 D 401/00 A 61 K 31/00			
The present search report has been drawn up for all claims			
Place of search	Date of completion of search	Examiner	
Berlin	09 October 90	VAN AMSTERDAM L.J.P.	
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